Prise en charge du choc septique: des recommandations à la pratique

B.LAMBERMONT

Rappel de la terminologie actuelle

Syndrome de réponse inflammatoire systémique (SIRS)	Température rectale > 38°C ou < 36°C, Tachycardie > 90 BPM, Polypnée > 20 cycles/mn ou PaCO2 < 32mmHg, Leucocytose > 12 000/mm3 ou <4000/mm3 ou > 10 % de formes immatures
Sepsis	Critères de SIRS et présence d'un foyer infectieux
Sepsis sévère	Sepsis et dysfonction d'au moins un organe : Hypotension (tension artérielle systolique < 90 mmHg ou réduction d'au moins 40 mmHg des chiffres habituels), acidose lactique, oligurie, encéphalopathie aiguë, hypoxémie inexpliquée, coagolupathie.
Choc septique	Sepsis sévère et hypotension persistante malgré un remplissage vasculaire adéquat et/ou nécessité de drogues inotropes ou vaso-actives

d'après ACCP et SCCM 1991

2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference

Mitchell M. Levy, MD, FCCP; Mitchell P. Fink, MD, FCCP; John C. Marshall, MD; Edward Abraham, MD; Derek Angus, MD, MPH, FCCP; Deborah Cook, MD, FCCP; Jonathan Cohen, MD; Steven M. Opal, MD; Jean-Louis Vincent, MD, FCCP, PhD; Graham Ramsay, MD; For the International Sepsis Definitions Conference

This document reflects a process whereby a group of experts and opinion leaders revisited the 1992 sepsis guidelines and found that apart from expanding the list of signs and symptoms of sepsis to reflect clinical bedside experience, no evidence exists to support a change to the definitions.

Crit Care Med 2003 Vol. 31, No. 4

Epidémiologie

- **Incidence annuelle du sepsis sévère: 3 cas pour 1000 habitants (18.000.000 cas par dans le monde)**
- **150.000 décès en Europe /an**
- **Incidence en USI:**
  - **Sepsis sévère-choc septique: 9-15%**
- **Mortalité: 40-65%**
- **40% des dépenses en USI**
- **7.6 milliards Euros en Europe**
- **16.7 milliards Euros aux USA en 2000**
- **50% des cas sont observés en dehors de la réa: importance de la sensibilisation à ce syndrome**

Incidence: évolution

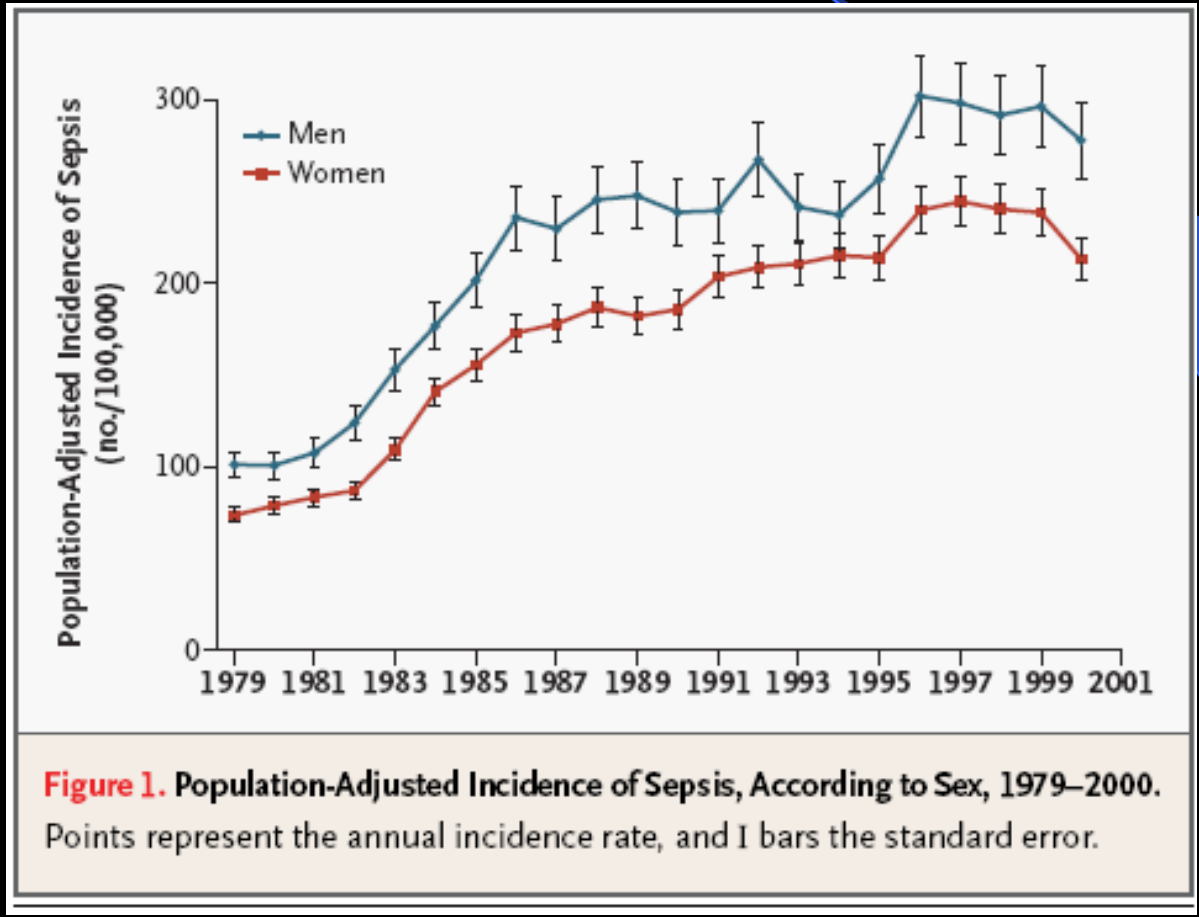


Figure 1. Population-Adjusted Incidence of Sepsis, According to Sex, 1979–2000.
Points represent the annual incidence rate, and I bars the standard error.

Martin GS N Eng J Med 2003

- Incidence en augmentation de 1.5% par an (en 2020 : 1.000.000 cas /an aux USA):
  - Procédures invasives
  - Vieillissement de la population (co-morbidités, actes invasifs, institutionalisation)
  - Fragilité de la population (HIV, diabète,greffes, etc..)

Germes en cause: évolution

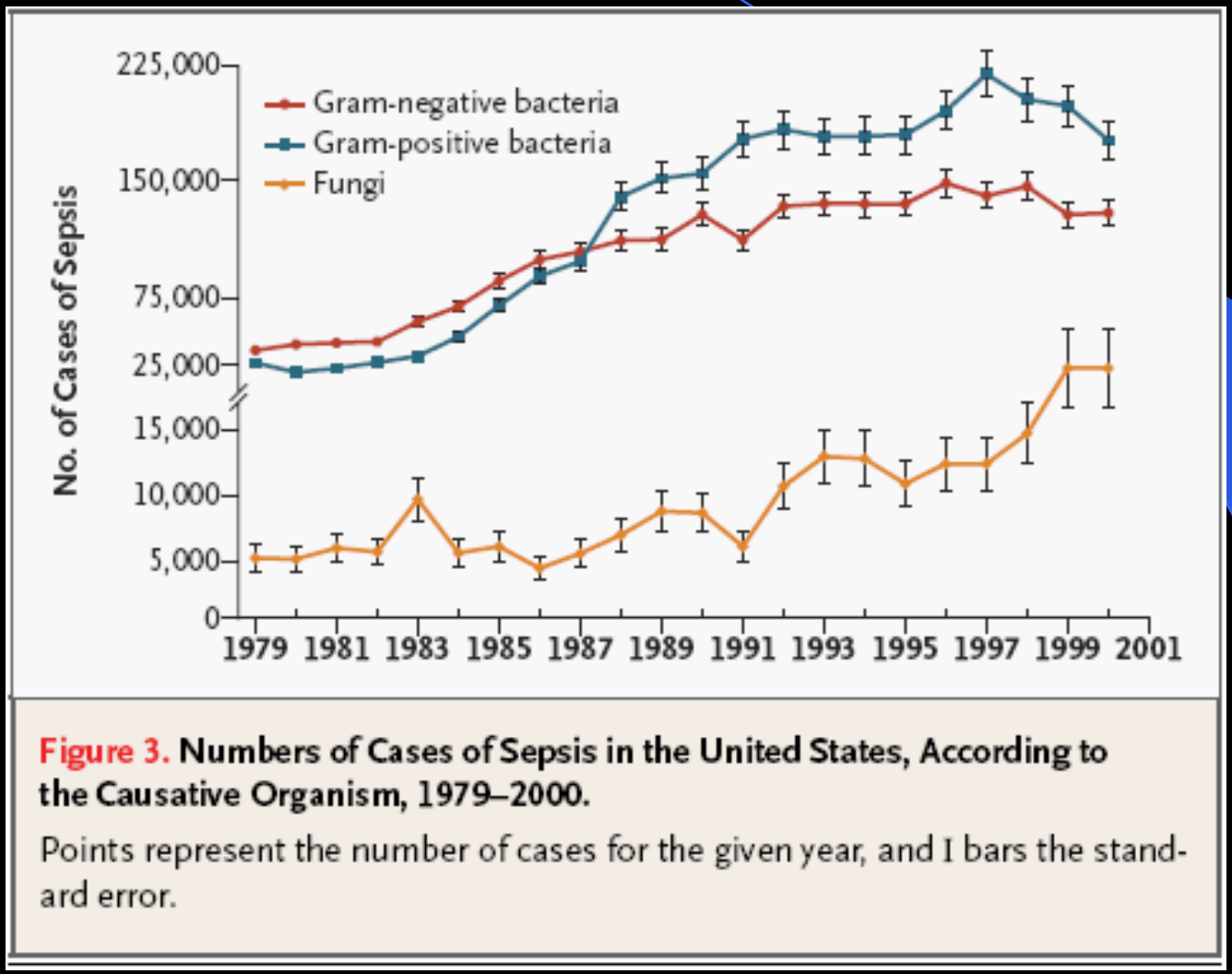


Figure 3. Numbers of Cases of Sepsis in the United States, According to the Causative Organism, 1979–2000.

Points represent the number of cases for the given year, and I bars the standard error.

Evolution de la mortalité

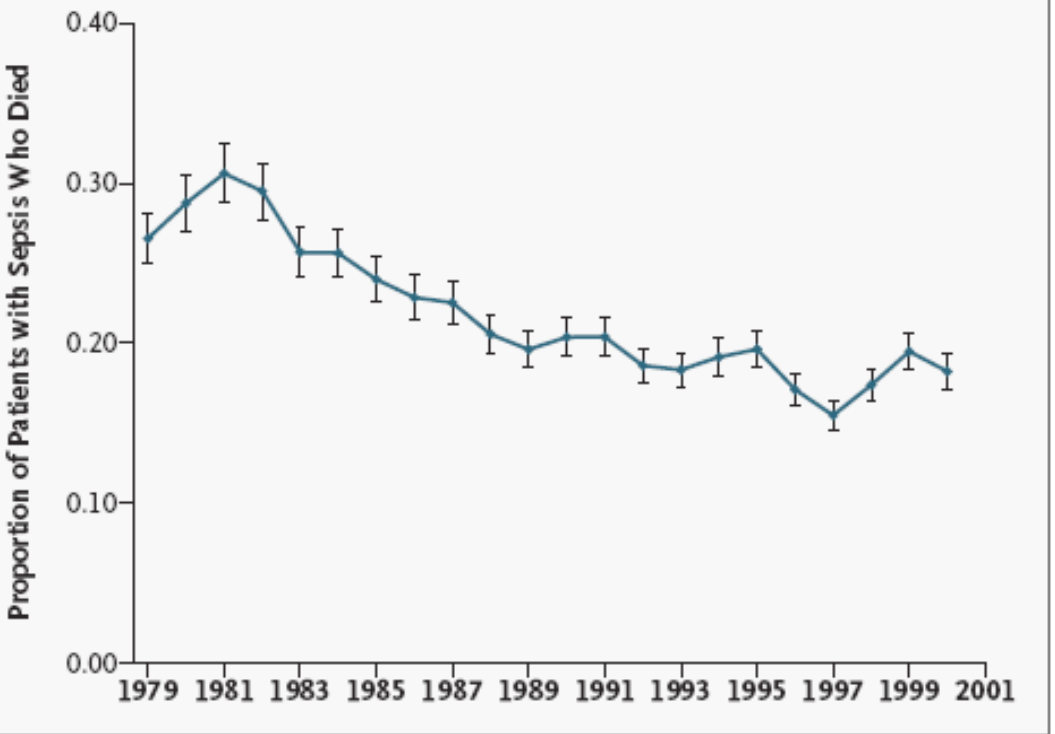


Figure 4. Overall In-Hospital Mortality Rate among Patients Hospitalized for Sepsis, 1979–2000.

Mortality averaged 27.8 percent during the first six years of the study and 17.9 percent during the last six years. The I bars represent the standard error.

Surviving Sepsis Campaign

A global program to:

Reduce mortality rates in severe sepsis

Sponsoring Organizations

- American Association of Critical Care Nurses
- American College of Chest Physicians
- American College of Emergency Physicians
- American Thoracic Society
- Australian and New Zealand Intensive Care Society
- European Society of Clinical Microbiology and Infectious Diseases
- European Society of Intensive Care Medicine
- European Respiratory Society
- International Sepsis Forum
- Society of Critical Care Medicine
- Surgical Infection Society

The surviving sepsis campaign: 1.Barcelona declaration 2002

- **Objectifs:**
  - **Réduire la mortalité du sepsis de 25% dans les 5 ans à venir**
- **Moyens:**
  1. **Information, sensibilisation: de la population, des gouvernements, des médecins**
  2. **Mise en place de guidelines**
  3. **Implémentation des guidelines**

2.Guidelines Committee*

Dellinger (RP)
Carlet
Masur
Gerlach
Levy
Vincent
Calandra
Cohen
Gea-Banacloche
Keh
Marshall
Parker

Ramsay
Zimmerman
Beale
Bonten
Brun-Buisson
Carcillo
Cordonnier
Dellinger (EP)
Dhainaut
Finch
Finfer
Fourrier

Harvey
Hazelzet
Hollenberg
Jorgensen
Maier
Maki
Marini
Opal
Osborn
Parrillo
Rhodes
Sevransky

Sprung
Torres
Vendor
Bennet
Bochud
Cariou
Murphy
Nitsun
Szokol
Trzeciak
Visonneau

Surviving Sepsis Campaign (SSC) Guidelines for Management of Severe Sepsis and Septic Shock

Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM and the

SSC Management Guidelines Committee

***Crit Care Med* 2004;32:858-873**
***Intensive Care Med* 2004;30:536-555**
available online at
www.springerlink.com
www.sccm.org
www.sepsisforum.com

Table 1. Grading system

Grading of recommendations

A. Supported by at least two level I investigations
B. Supported by one level I investigation
C. Supported by level II investigations only
D. Supported by at least one level III investigation
E. Supported by level IV or V evidence

Grading of evidence

I. Large, randomized trials with clear-cut results; low risk of false-positive (alpha) error of false-negative (beta) error
II. Small, randomized trials with uncertain results; moderate-to-high risk of false-positive (alpha) and/or false-negative (beta) error
III. Nonrandomized, contemporaneous controls
IV. Nonrandomized, historical controls and expert opinion
V. Case series, uncontrolled studies, and expert opinion

- Recommandations groupées par catégorie et non par ordre d'importance
- Classement des recommandations implique un support de la littérature et pas un ordre de priorité

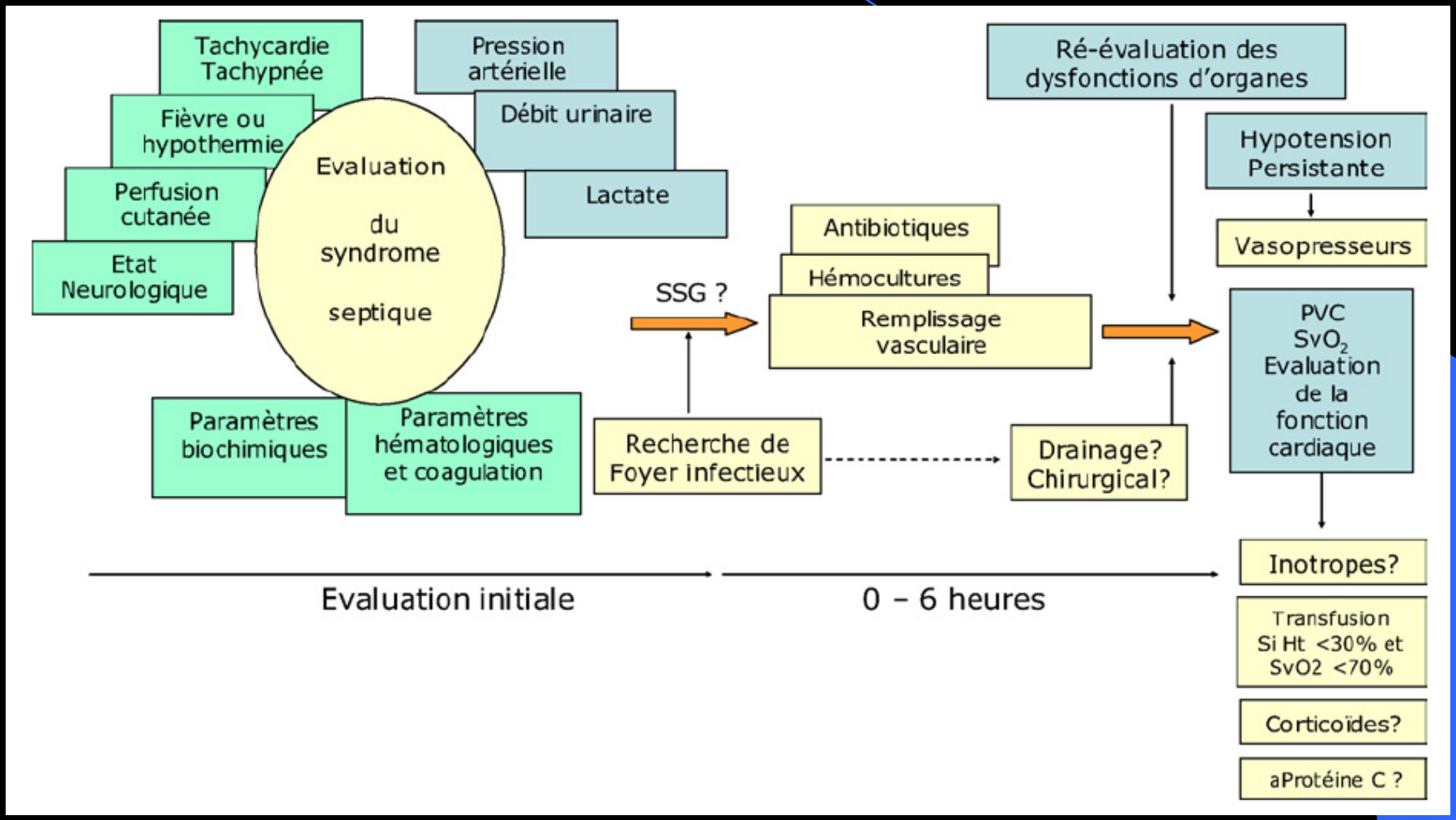
3.Implémentation des guidelines

- Sepsis ***bundles*** : petit groupe de recommandations simples visant à améliorer la prise en charge
  - Sepsis resuscitation bundle
  - Sepsis management bundle

www.survivingsepsis.org

www.IHI.org

Aspects pratiques de la prise en charge



1. Identification précoce

- Identification précoce = traitement précoce = meilleur pronostic
- Patient en choc septique: facile à identifier
- MAIS identification des patients en sepsis à risque de sepsis sévère ou choc septique difficile:
  - Comment suspecter l'existence d'un problème infectieux?
  - Critères permettant de définir avec certitude l'existence d'un sepsis
  - Comment identifier les patients en sepsis à risque d'évoluer vers sepsis sévère ou choc septique?

- 80% des patients en USI = SIRS, dont 26% développent sepsis , 18% sepsis sévère, 4% choc septique
- 71% des patients en choc septique étaient en sepsis sévère la veille
- Mortalité à 28 JOURS:
  - SIRS 7%
  - SEPSIS: 10-15%
  - SEPSIS SEVERE: 20- 30%
  - CHOC SEPTIQUE: 40-50%

Identification des patients en sepsis sévère ou choc septique

- Identification précoce des signes de dysfonction d'organe

Les 90 premières minutes

1. **La fonction circulatoire :**
   - Hypotension systolique <90 mm Hg (ou baisse de 40 mm Hg par rapport au chiffre de base) ou moyenne <65 mm Hq (ou PA diastolique <40 mm Hq);
   - Hyperlactatémie artérielle >2 mmoles/L (ou >1,5 x la normale)
   - Chez le malade sous surveillance hémodynamique, apparition d'un état hyperdynamique (i.e., augmentation de l'index cardiaque >3.5 L/min.m^2)
2. **La fonction respiratoire :**
   - PaO_2 <60 mm Hg ou SpO_2 <90% à l'air (a fortiori sous O_2)
   - Ou PaO_2/FiO_2 <300, ou baisse de ce rapport de >20% chez le malade sous assistance ventilatoire
3. **Les fonctions supérieures :** présence d'une encéphalopathie ou syndrome confusionnel, qui peut se traduire par un score de Glasgow <14.
4. **La fonction rénale :**
   - Oligurie <0.5 ml/kg.h, persistante pendant 3 heures malgré le remplissage
   - Créatinine > 177 µmol/L (20 mg/L), ou élévation de +50% par rapport au chiffre de base
5. **La coaqulation :**
   - Thrombopénie <100,000 /mm^3 ou TP <50%, ou chute de >30% de la concentration des plaquettes ou du TP lors de 2 prélèvements successifs
   - Ou score de CIVD (ISTH) >4 [20,21]
6. **La fonction hépatique :**
   - Hyperbilirubinémie >34 µmol/L

2.Prise en charge sepsis sévère-choc septique

- En cas de détresse vitale orientation immédiate vers l'USI si nécessaire
- **Surveillance**: oxymétrie de pouls, FC, PA non invasive, FR, diurèse
- **Prélèvements** sanguins nécessaires (bio, gazo, hémoc, lactate, etc..)
- **Oxygénothérapie** systématique avec SpO2 > 95%
- Si d'emblée PA sys < 70 ou DIAS < 40 associer d'emblée un vasopresseur
- **Remplissage** vasculaire: 500 ml cristalloïdes en 10-15 min renouvelés jusque 60 ml/kg pour obtenir PAmoy > 65
- Appel du médecin référent pour évaluation des sepsis sévères pour décider de **l'ABth** probabiliste à ce stade

3.Evaluation de la réponse au remplissage

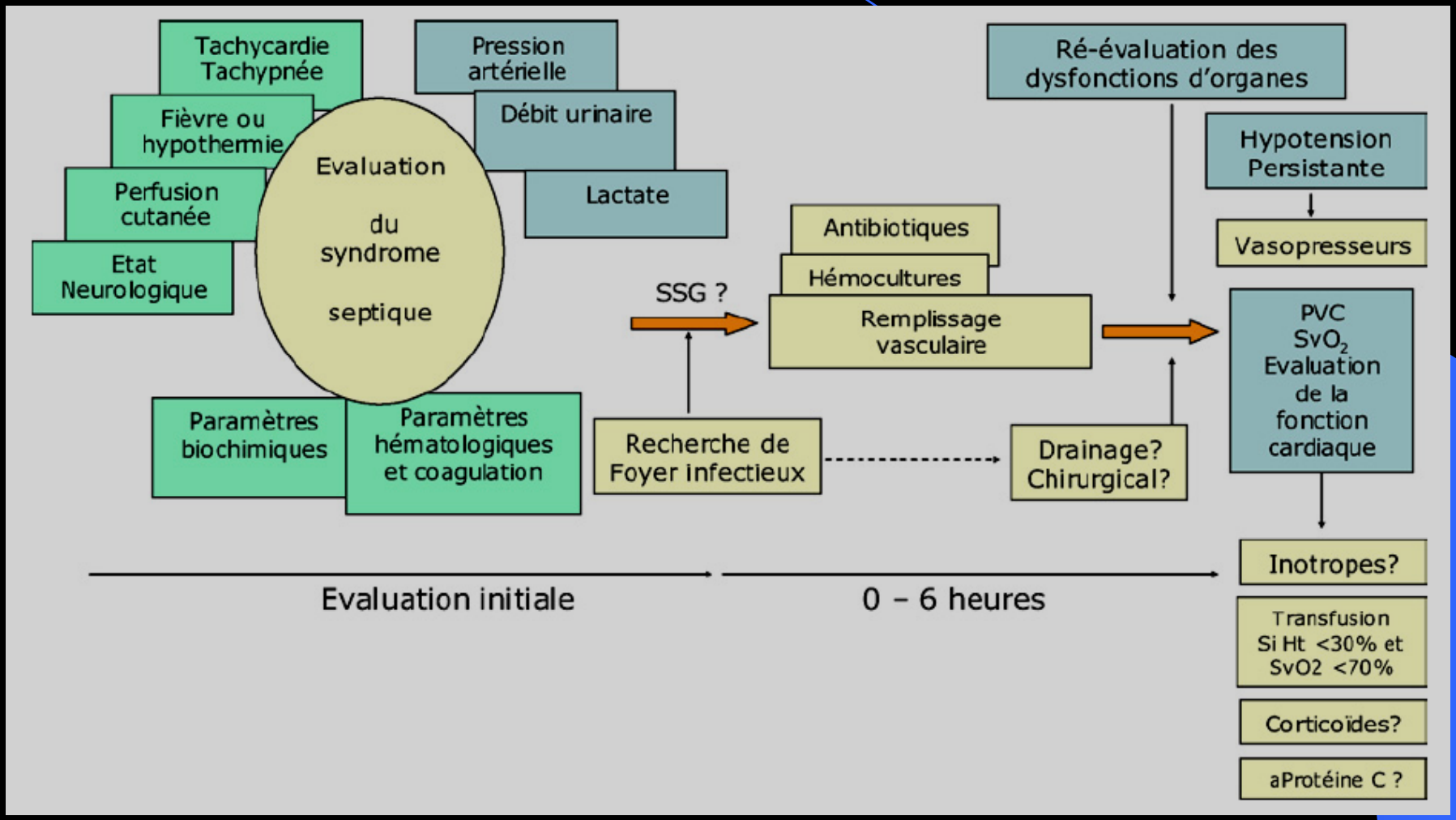
- Réponse au remplissage: amélioration perfusion tissulaire, diurèse > 0.5 ml/kg/h, PAM> 65, absence de comorbidité significative, identification claire du foyer

=> Sepsis sévère rapidement résolutif: middle care

- Persistence des signes d'hypoperfusion : marbrure, lactate > 4 mEq/L, dysfonction d'organe

=> Choc septique: réanimation

Aspects pratiques de la prise en charge



Au cours des 6 premières heures

- Objectifs hémodynamiques
- Investigations complémentaires
- Traitement

Objectifs

- Objectifs hémodynamiques:
  - Disparition des signes d'hypoperfusion: marbrure, sudation, froideur cyanose des extrémités
  - PAM > 65 mmHg
  - SV02 > 70% (détection d'une chute de débit ou anémie sévère)
  - DIURESE > 0.5 ml/kg/h
  - Hb: > 8-9

Investigations complémentaires

- SI objectifs non atteints évaluation de la réserve de précharge et de la fonction cardiaque:
  - Indices statiques: pression (voir CCM 2007 Osman), volume (échographie, PICCO), débit cardiaque.
  - Indices dynamiques (voir indices écho (ett, eto, variation PA, VVS, doppler oesophagien))

Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge*

David Osman, MD; Christophe Ridel, MD; Patrick Ray, MD; Xavier Monnet, MD, PhD; Nadia Anguel, MD; Christian Richard, MD; Jean-Louis Teboul, MD, PhD

Objective: Values of central venous pressure of 8–12 mm Hg and of pulmonary artery occlusion pressure of 12–15 mm Hg have been proposed as volume resuscitation targets in recent international guidelines on management of severe sepsis. By analyzing a large number of volume challenges, our aim was to test the significance of the recommended target values in terms of prediction of volume responsiveness.

Design: Retrospective study.

Setting: A 24-bed medical intensive care unit.

Patients: All consecutive septic patients monitored with a pulmonary artery catheter who underwent a volume challenge between 2001 and 2004.

Intervention: None.

Measurements and Main Results: A total of 150 volume challenges in 96 patients were reviewed. In 65 instances, the volume challenge resulted in an increase in cardiac index of ≥15% (responders). The pre-infusion central venous pressure was similar in responders and nonresponders (8 ± 4 vs. 9 ± 4 mm Hg). The pre-infusion pulmonary artery occlusion pressure was slightly lower in responders (10 ± 4 vs. 11 ± 4 mm Hg, $p < .05$). However, the significance of pulmonary artery occlusion pressure to predict fluid responsiveness was poor and similar to that of central venous pressure, as indicated by low values of areas under the receiver operating characteristic curves (0.58 and 0.63, respectively). A central venous pressure of <8 mm Hg and a pulmonary artery occlusion pressure of <12 mm Hg predicted volume responsiveness with a positive predictive value of only 47% and 54%, respectively. With the knowledge of a low stroke volume index (<30 $mL \cdot m^{-2}$), their positive predictive values were still unsatisfactory: 61% and 69%, respectively. When the combination of central venous pressure and pulmonary artery occlusion pressure was considered instead of either pressure alone, the degree of prediction of volume responsiveness was not improved.

Conclusion: Our study demonstrates that cardiac filling pressures are poor predictors of fluid responsiveness in septic patients. Therefore, their use as targets for volume resuscitation must be discouraged, at least after the early phase of sepsis has concluded. (Crit Care Med 2007; 35:64–68)

KEY WORDS: central venous pressure; pulmonary artery occlusion pressure; volume challenge; volume responsiveness; septic shock

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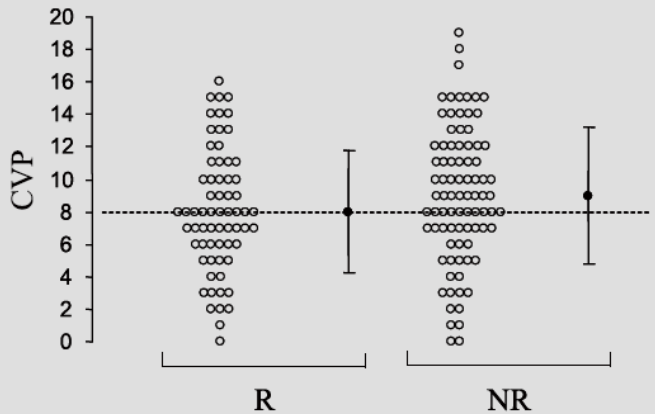


Figure 2. Individual values (*open circles*) and mean ± SD (*closed circles*) of pre-infusion central venous pressure (*CVP*) (both expressed in millimeters of mercury) in responders (*R*) and nonresponders (*NR*).

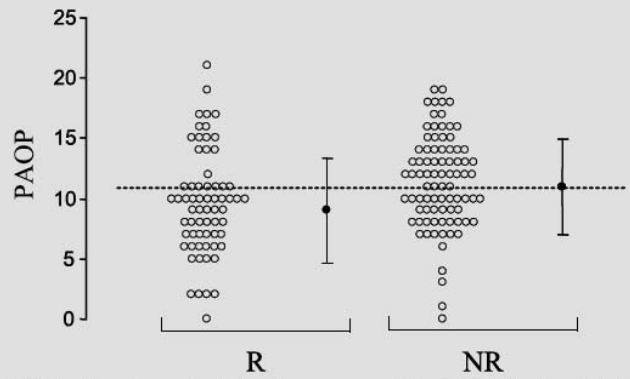


Figure 3. Individual values (*open circles*) and mean ± SD (*closed circles*) of pre-infusion pulmonary artery occlusion pressure (*PAOP*) (both expressed in millimeters of mercury) in responders (*R*) and nonresponders (*NR*).

Une PVC < 8 ou une wedge < 12 ont une valeur prédictive positive de réponse au remplissage de 47 et 54% respectivement!

Crit Care Med 2007 Vol. 35, No. 1

Indices dynamiques

		Variabilité respiratoire sous <u>Ventilation mécanique</u>
INVASIF	ΔPAS	> 10 mmHg ou 9%
	VVS	> 10%
	ΔPP	>12%
ECHO	ΔVélocité aortique	>12%
	ΔVCId	>12%
	Diminution inspi de VCS	>36%
	Lever de jambe passif	
	ΔPP	> 10%
	Δdébit aort	>10%

Les 6 premières heures

Traitement

- Remplissage (cfr Rivers 2001)
- Ventilation mécanique
- Adaptation ABth
- Drainage foyer (chirurgical si néc)
- Amines vasopressives
- Inotropes positifs

Les agents vasopresseurs et les agents inotropes

- Amines vasopressives indiquées en l'absence d'obtention des objectifs de PAM et ou de diurèse fixés
- Si PAsys < 70 ou PAdias < 40 d'emblée => vasopresseurs d'emblée
- Tt inotrope: si objectifs non atteints en fct° des résultats des investigations complémentaires

Le choix des vasopresseurs

- Adrénaline
- Dopamine
- Levophed
- vasopressine

Adrénaline

- Effets métaboliques importants (hormone de stress):
  - Vasoconstriction splanchnique
  - Augmentation de la consommation d'oxygène et de la production de lactate
- Méta-analyse vs dobu-NA: pas différence (Mullner et al. Cochrane data base Syst Rev 2004)
- Etude **CATS** (Annane 36th SCCM): 330 patients en choc septique: adrénaline vs NA-dobutamine: Pas de différence en terme de survie ou d'effets indésirables

Dopamine

- Surtout efficace par une augmentation de débit
- Moins efficace que noradrénaline dans les chocs vasoplégiques
- A partir de 20 µg/kg/min tachycardie importante.
- Pas d'intérêt à dose « rénale »

Noradrénaline

- Effet principalement vasoconstricteur
- Plus puissant vasoconstricteur que la dopamine (Martin et al. Chest 1993)
- Agit plus sur artériole efférente que afférente du rein: effet bénéfique sur la diurèse
- D'emblée si PAS < 70 ou PAD < 40 ou après expansion volémique suffisante si PAM < 65

Vasopressine

- Au cours du choc septique:
  - Diminution de production endogène
  - Mais augmentation au cours de l'administration exogène
- Etude VASST(Vasopressin in Septic Shock Trial, Russel et al. 36th SCCM): 779 patients en choc septique: NA vs VSP
- Choc septique réfractaire

Dobutamine

- A n'utiliser que quand volémie optimalisée si persistence de débit cardiaque bas objectivé par SVO2 basse, en l'absence d'anémie.
- Pas d'intérêt à l'utiliser pour obtenir des valeurs supra normales de DO2

Moyens à mettre en œuvre (1)

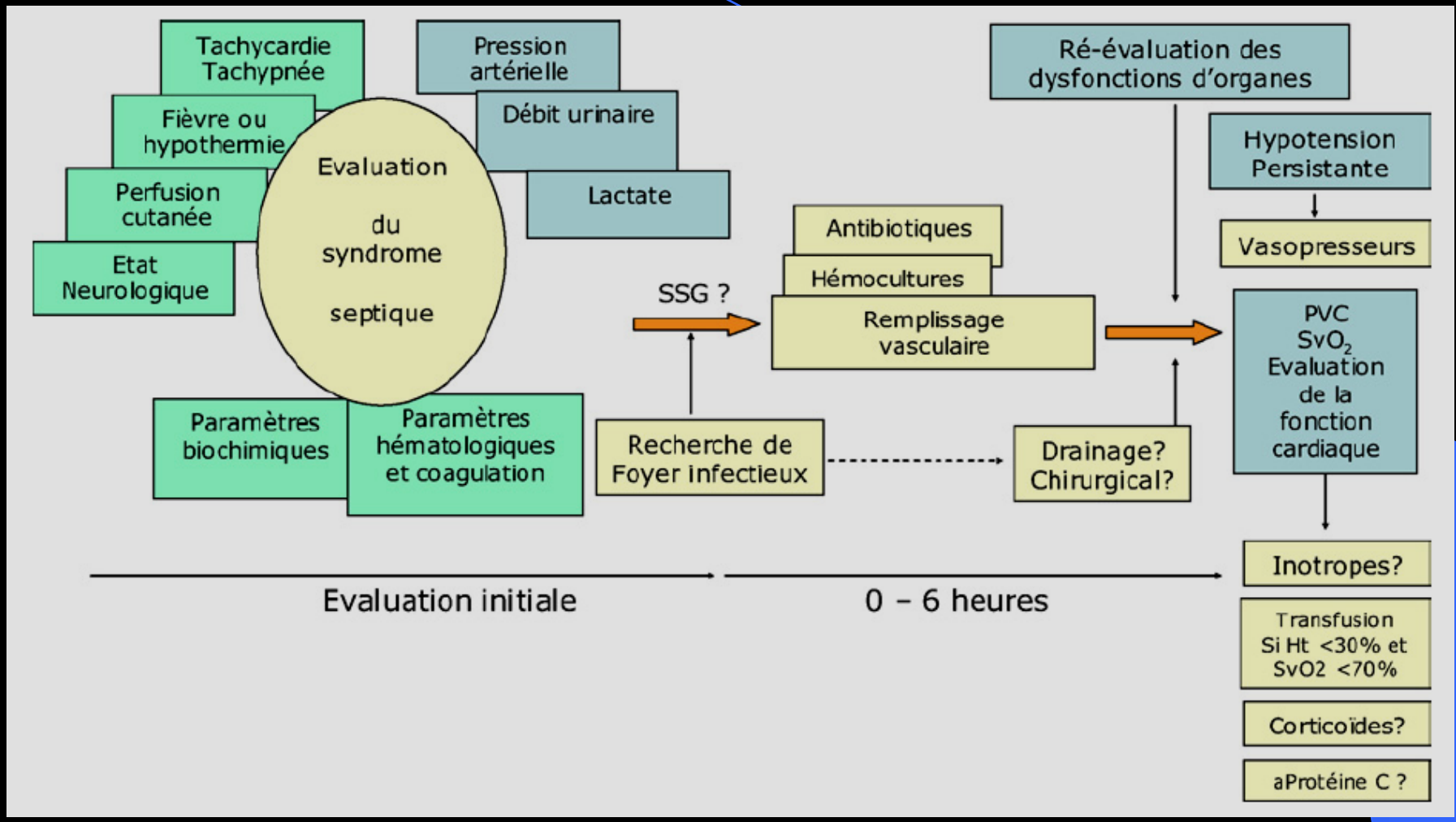
- Voie centrale:
  - Perfusion fiable des drogues
  - Mesure de la SVcO2
  - Mesure de la PVC
- Cathéter artériel:
  - Meilleur contrôle de la PA en cas de choc
  - Gazométrie
  - Indices dynamiques de précharge
- Examens biologiques:
  - Contrôle avant la 6^{e} heure de: SVO_2, Hb, lactate

Moyens à mettre en œuvre (2)

- Monitoring de la fonction cardiaque:
  - Selon les compétences: swan, Picco, echocardiaque
- Contrôle du foyer infectieux:
  - Imagerie médicale
  - Ponction
  - Chirurgie

Objectifs pour les 6 premières heures: sepsis resuscitation bundle

- Lactate
- Hémocultures avant administration antibiotiques
- Antibiothérapie probabiliste (dans les 3h)
- Si hypotension (PAS < 90 ou PAM < 70) ou lactate > 4 mmol/L
  - Expansion volémique
  - Vasopresseurs si PAM < 65 malgré expansion volémique
- Si hypotension ou lactate persiste:
  - Maintenir PVC 8-12 (préférer indices dynamiques)
  - Inotrope (si Htc < 30% => d'abord transfusion), si SVcO2 < 70%, SvO2 < 65% et PVC > 8 mmHg


Tachycardie
Tachypnée
Fièvre ou hypothermie
Perfusion cutanée
Etat Neurologique
Evaluation du syndrome septique
Pression artérielle
Débit urinaire
Lactate
Paramètres biochimiques
Paramètres hématologiques et coagulation
SSG ?
Recherche de Foyer infectieux
Antibiotiques
Hémocultures
Remplissage vasculaire
Drainage? Chirurgical?
Ré-évaluation des dysfonctions d'organes
Hypotension Persistante
Vasopresseurs
PVC
SvO2
Evaluation de la fonction cardiaque
Inotropes?
Transfusion Si Ht <30% et SvO2 <70%
Corticoïdes?
aProtéine C ?
Evaluation initiale
0 – 6 heures

Dans les premières 24 heures

- Objectifs thérapeutiques des 6 premières heures
- Sepsis management bundle:
  - Corticoïdes low dose
  - Protéine C
  - Contrôle de la glycémie (< 150 mg/dl)
  - Ventilation protectrice (Pplat < 30 cmH2O)
- Adaptation ABth
- Diminution des vasopresseurs
- Soins standards:
  - Prophylaxie TVP
  - Prévention ulcère de stress
  - Nutrition
  - Epuration extra-rénale

Give your patient a fast hug (at least) once a day*

Jean-Louis Vincent, MD, PhD, FCCM

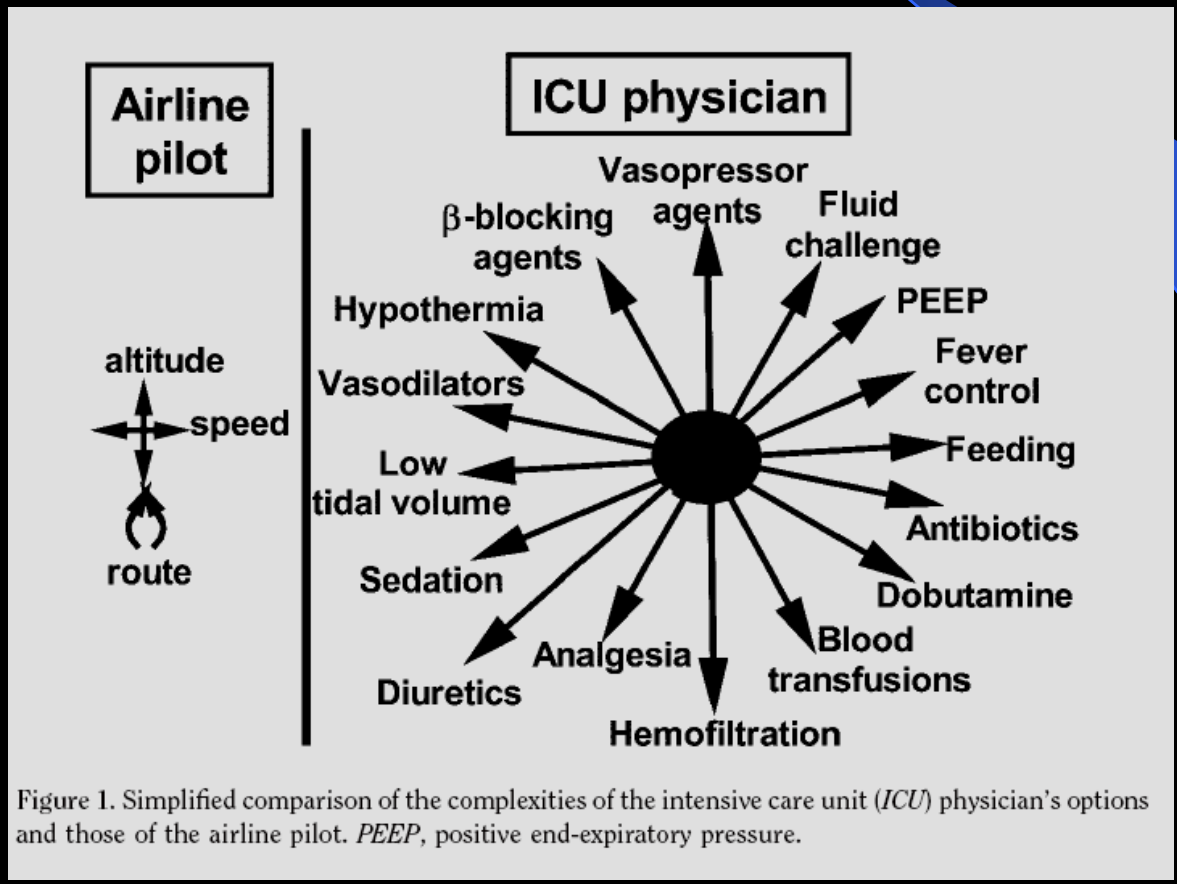


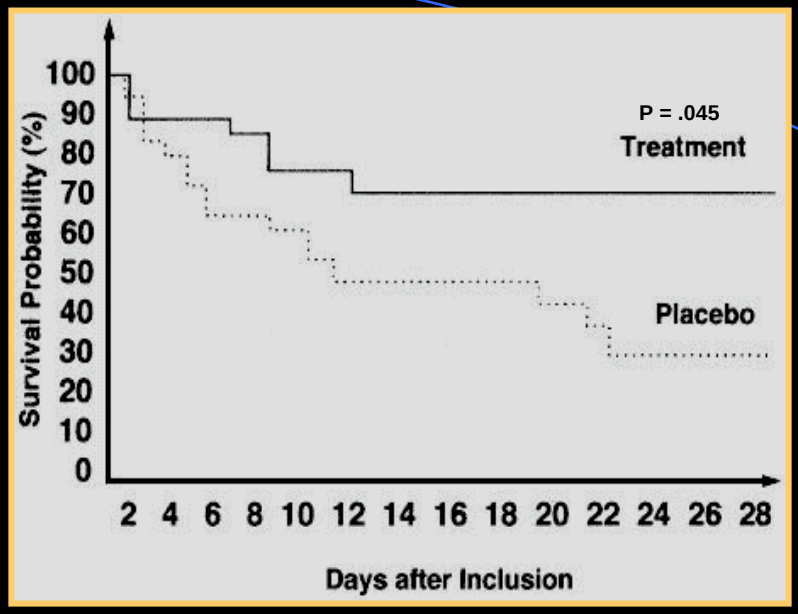
Figure 1. Simplified comparison of the complexities of the intensive care unit (*ICU*) physician's options and those of the airline pilot. *PEEP*, positive end-expiratory pressure.

Table 1. The seven components of the Fast Hug approach

Component	Consideration for Intensive Care Unit (ICU) Team
Feeding	Can the patient be fed orally, if not enterally? If not, should we start parenteral feeding?
Analgesia	The patient should not suffer pain, but excessive analgesia should be avoided
Sedation	The patient should not experience discomfort, but excessive sedation should be avoided; "calm, comfortable, collaborative" is typically the best level
Thromboembolic prevention	Should we give low-molecular-weight heparin or use mechanical adjuncts?
Head of the bed elevated	Optimally, 30° to 45°, unless contraindications (e.g., threatened cerebral perfusion pressure)
Stress Ulcer prophylaxis	Usually H_2 antagonists; sometimes proton pump inhibitors
Glucose control	Within limits defined in each ICU

Les corticoïdes dans le choc septique

- Doses pharmacologiques abandonnées dans les années 80’
- Mécanismes action corticoides dans le choc septique:
  - Diminution de la production de NO
  - Augmentation de l’expression des récepteurs aux catécholamines désensibilisés par feed back négatif lié aux taux circulants élevés de catécholamines
  - Inhibition de la production locale de médiateurs inflammatoires



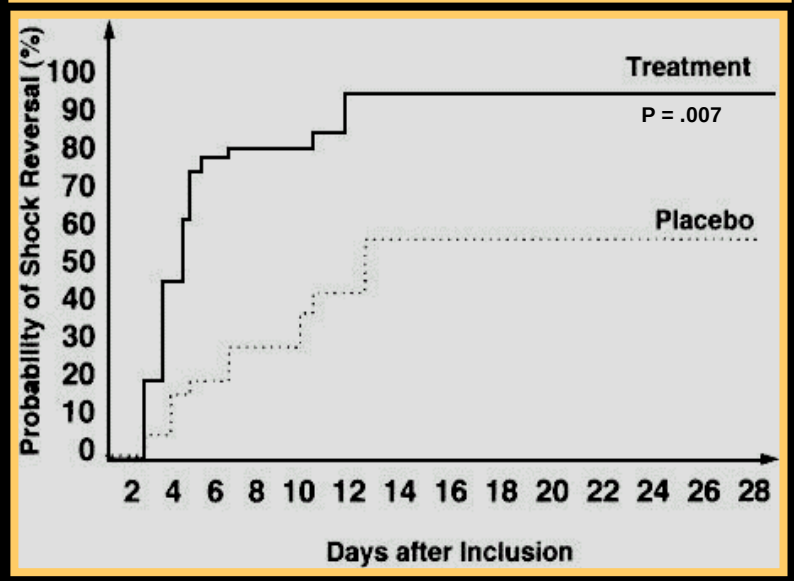
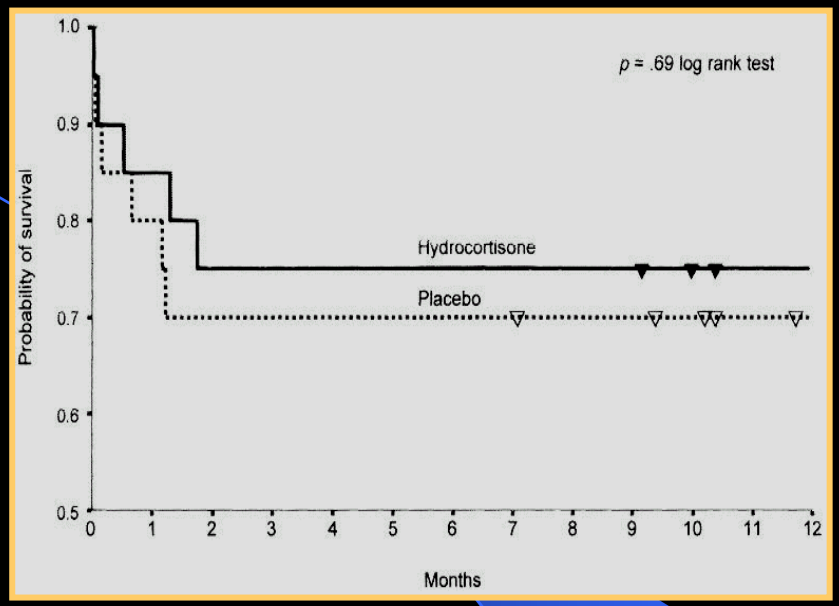


Figure 2 and Figure 3, page 648, reproduced with permission from Bollaert PE, Charpentier C, Levy B, et al. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. *Crit Care Med 1998; 26:645-650*



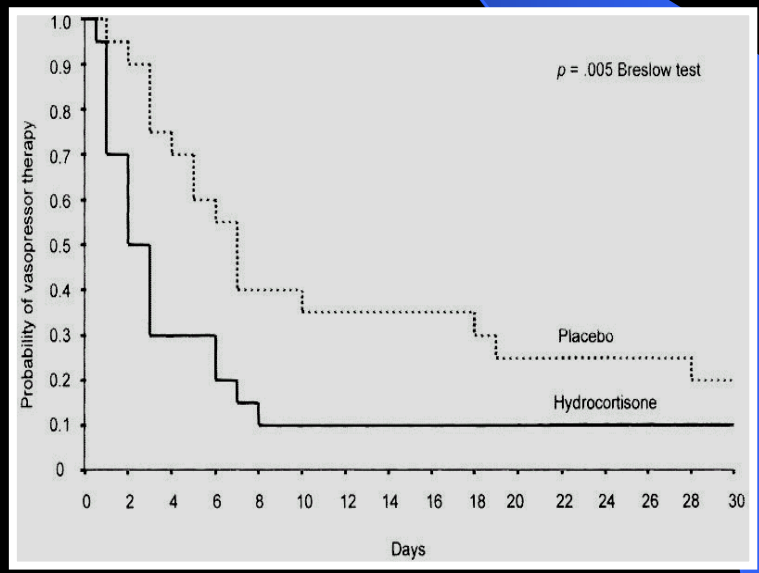


Figure 2 and Figure 3, page 727, reproduced with permission from Briegel J, Forst H, Haller M, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: A prospective, randomized, double-blind, single-center study. *Crit Care Med* 1999; 27:723-732

Insuffisance surrénalienne

- Mise en évidence que insuffisance surrénalienne est associée à un mauvais pronostic dans le choc septique (D Annane, JAMA, 2000)
- Absolue (0-3%): cortisol total < 150 µg/L
- Relative (70% dans étude de Annane): test au synacthen (250µg), cortisol augmente de < 90 µg/L
- Cortisol > 340 µg/L: possibilité de résistance périphérique aux corticoides
- Si albumine < 25 g/L : cortisol libre
  - Insuf surrénalienne: < 20 µg/l
  - Test ACTH: augmentation < 31 µg/l

Annane D, Sébille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002; 288:862-871

- Randomisée, double aveugle, vs placebo, multicentrique
- 300 patients en choc septique après un test ACTH

Mortalité à J28

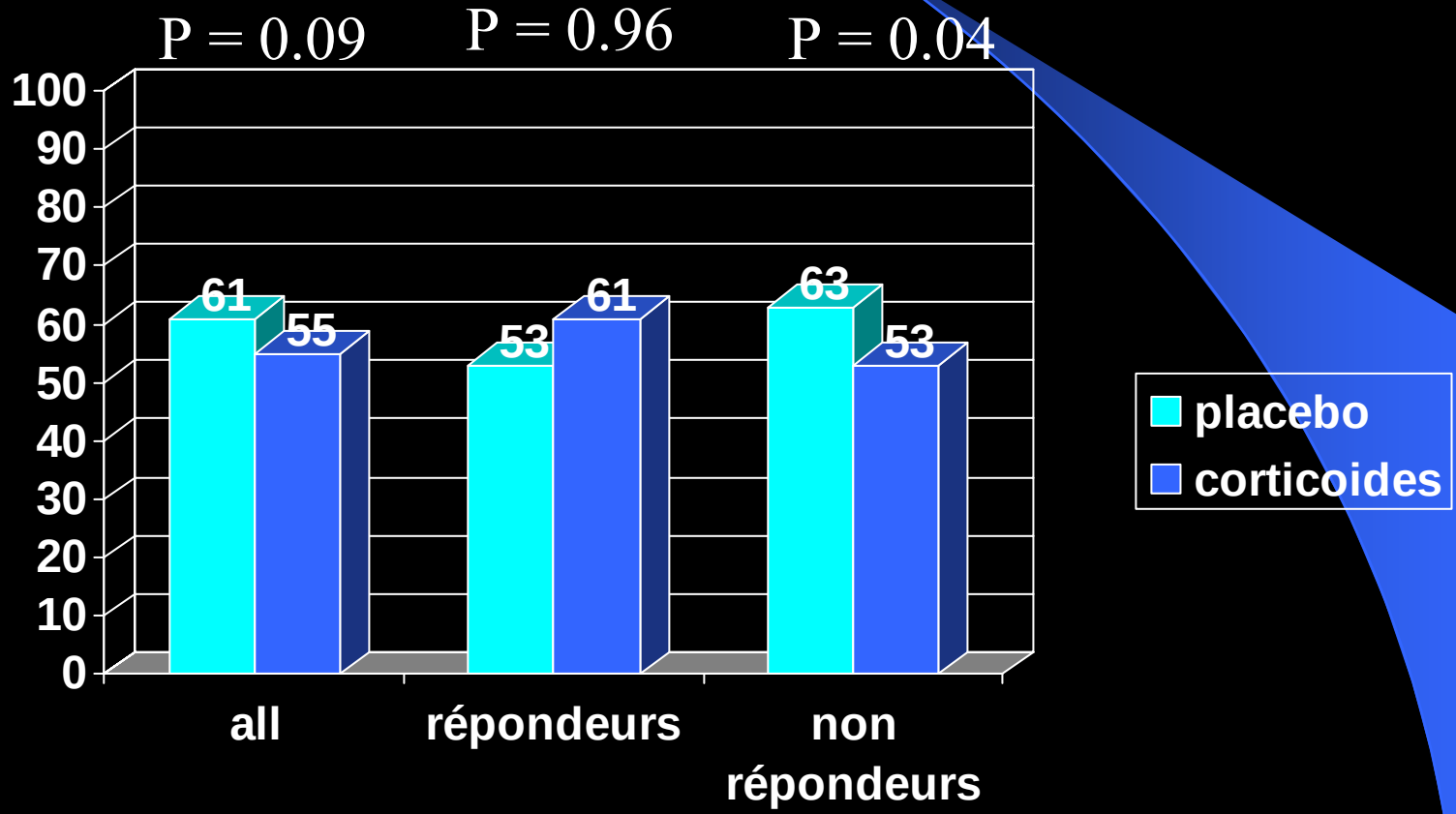


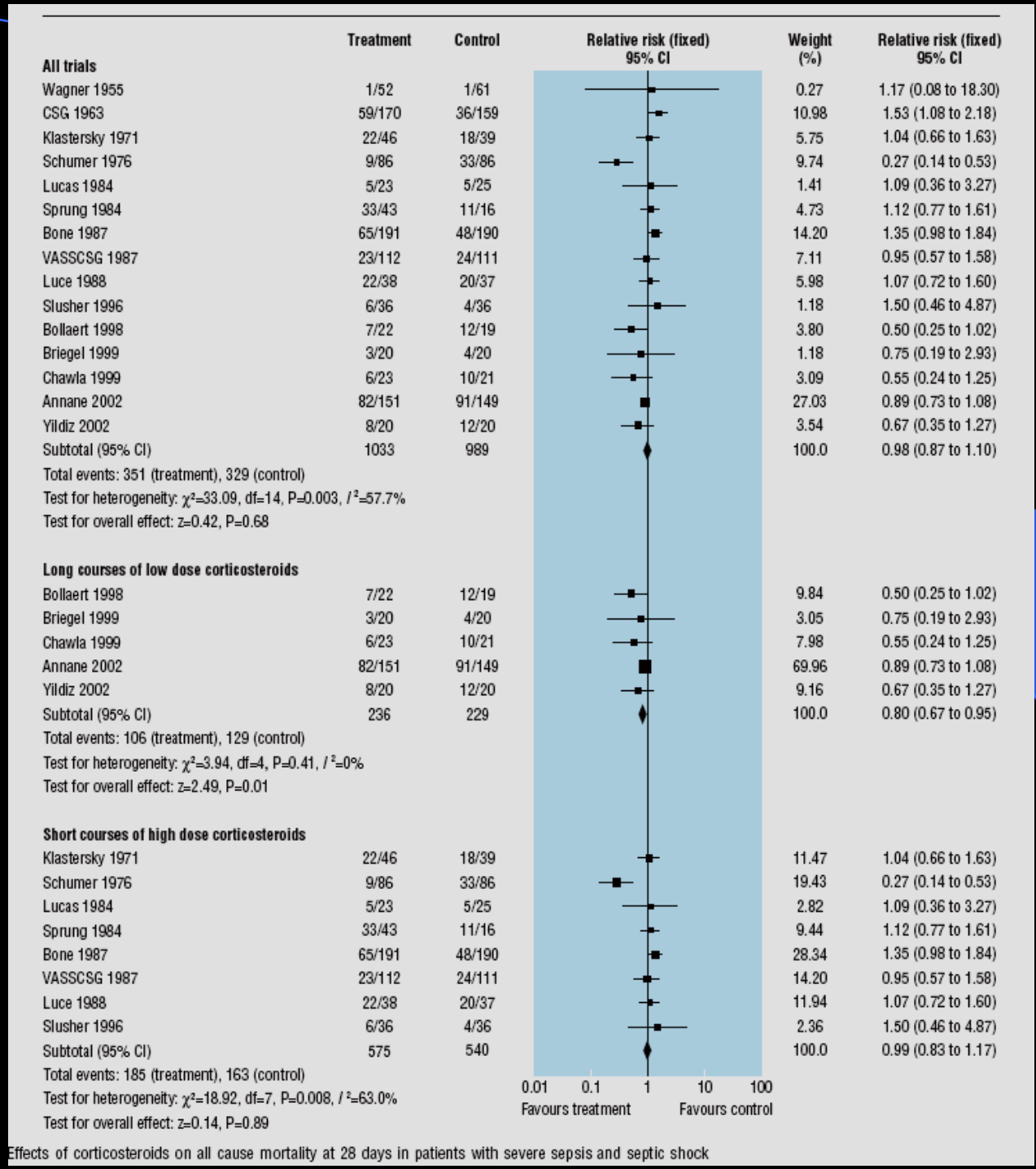
Table 4. Frequency of Fatal Events in 299 Patients with Septic Shock*

Variable	No. (%)		Adjusted OR (95% CI)	*P* Value
	Placebo	Steroids		
		Nonresponders		
No. of patients	115	114		
28-day mortality	73 (63)	60 (53)	0.54 (0.31-0.97)	.04
ICU mortality	81 (70)	66 (58)	0.50 (0.28-0.89)	.02
Hospital mortality	83 (72)	70 (61)	0.53 (0.29-0.96)	.04
1-Year mortality	88 (77)	77 (68)	0.57 (0.31-1.04)	.07
		Responders		
No. of patients	34	36		
28-Day mortality	18 (53)	22 (61)	0.97 (0.32-2.99)	.96
ICU mortality	20 (59)	24 (67)	0.99 (0.31-3.16)	.99
Hospital mortality	20 (59)	25 (69)	1.20 (0.38-3.76)	.75
1-Year mortality	24 (71)	25 (69)	0.70 (0.20-2.40)	.57
		All Patients		
No. of patients	149	150		
28-Day mortality	91 (61)	82 (55)	0.65 (0.39-1.07)	.09
ICU mortality	101 (68)	90 (60)	0.61 (0.37-1.02)	.06
Hospital mortality	103 (69)	95 (63)	0.67 (0.40-1.12)	.12
1-Year mortality	112 (75)	102 (68)	0.62 (0.36-1.05)	.08

*Results are based on patient responses to a short corticotropin test. Using baseline cortisol, cortisol response, McCabe classification, Logistic Organ Dysfunction score, arterial lactate levels and Pao_2/Fio_2 results for adjustment, analyses were performed with use of logistic models. OR indicates, odds ratios; CI, confidence intervals; and ICU, intensive care unit.

Meta analyse

Annane BMJ 2004 Corticosteroid for severe sepsis and septic shock: A systematic review and meta analysis



Effects of corticosteroids on all cause mortality at 28 days in patients with severe sepsis and septic shock

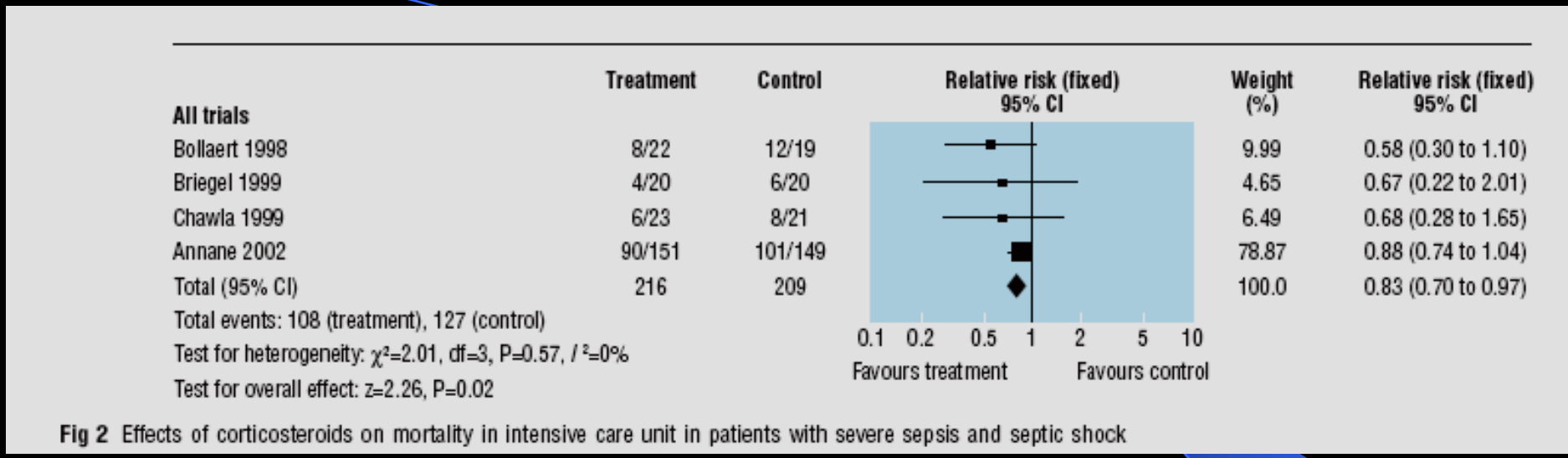


Fig 2 Effects of corticosteroids on mortality in intensive care unit in patients with severe sepsis and septic shock

- Réduction de mortalité : NNT= 9

Annane BMJ 2004 Corticosteroid for severe sepsis and septic shock: A systematic review and meta analysis

What is already known

Short courses of high dose corticosteroids do not affect mortality from severe sepsis and septic shock

---

Long courses of low dose corticosteroids improve systemic haemodynamics and reduce the time on vasopressor treatment

What this paper adds

Long courses of low dose corticosteroids reduce mortality at 28 days, in intensive care units, and in hospital

---

Long courses of low dose corticosteroids do not significantly alter the risk of gastroduodenal bleeding, superinfections, or hyperglycaemia

Annane BMJ 2004 Corticosteroid for severe sepsis and septic shock: A systematic review and meta analysis

Recommendations

We cannot provide definite recommendations for the selection of patients who might most benefit from corticosteroid. Separate data for adrenal insufficiency were available in only two studies.[9 12] However, different definitions for adrenal insufficiency were used. In the first trial, too few patients had adrenal insufficiency to draw any conclusion.[9] In the second trial, a benefit from corticosteroids was shown only in patients with a cortisol increase after adrenocorticotropin hormone ≤ 248 nmol/l.[12] The weight of this trial in the meta-analysis was about 70%. Until there is further research on optimising diagnostic testing of adrenal insufficiency in patients with septic shock, corticosteroids should be given only to patients with a random cortisol concentration ≤ 414 nmol/l (that is, absolute adrenal insufficiency) or a cortisol response to adrenocorticotropin hormone ≤ 248 nmol/l (that is, relative adrenal insufficiency).[86]

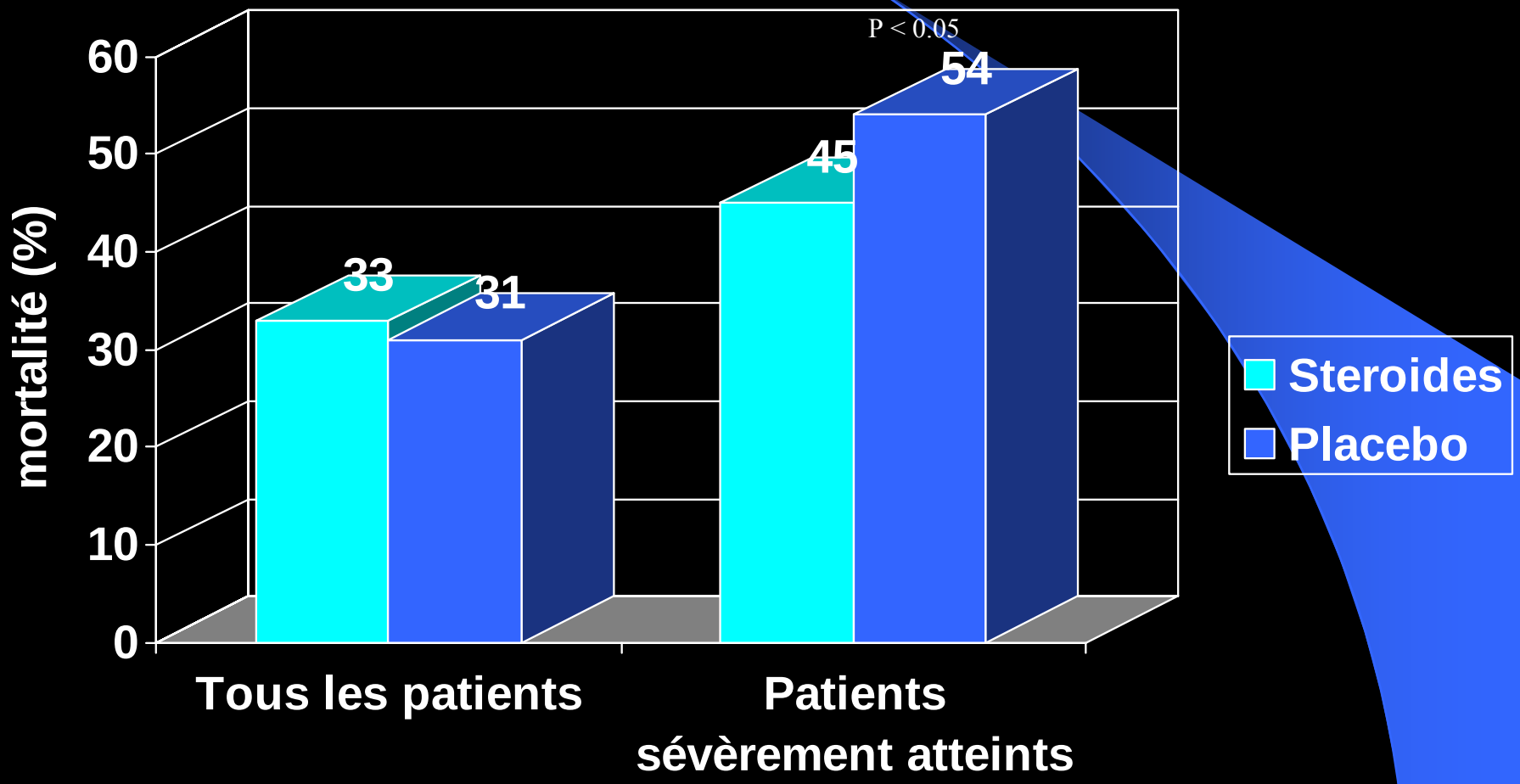
In conclusion, hydrocortisone (or equivalent) should be given to patients with septic shock immediately after they undergo an adrenocorticotropin hormone test, at a dose of 200-300 mg, and should be continued for 5-11 days, only when absolute or relative adrenal insufficiency is present.

Annane BMJ 2004 Corticosteroid for severe sepsis and septic shock: A systematic review and meta analysis

Etude corticus

- 500 patients: comparaison corticothérapie vs placebo
- Taux de cortisol basal: relation non linéaire avec mortalité (mortalité plus élevée pour patients avec taux très bas ou très élevé)
- Répondeurs au test synacthen : mortalité plus faible
- Mortalité pas influencée par administration de corticoides mais bien le nombre de défaillance d'organes et sortie plus rapide du choc
- Patients traités ont plus: hyperglycémie, recurrent septic shock, nosocomial sepsis.

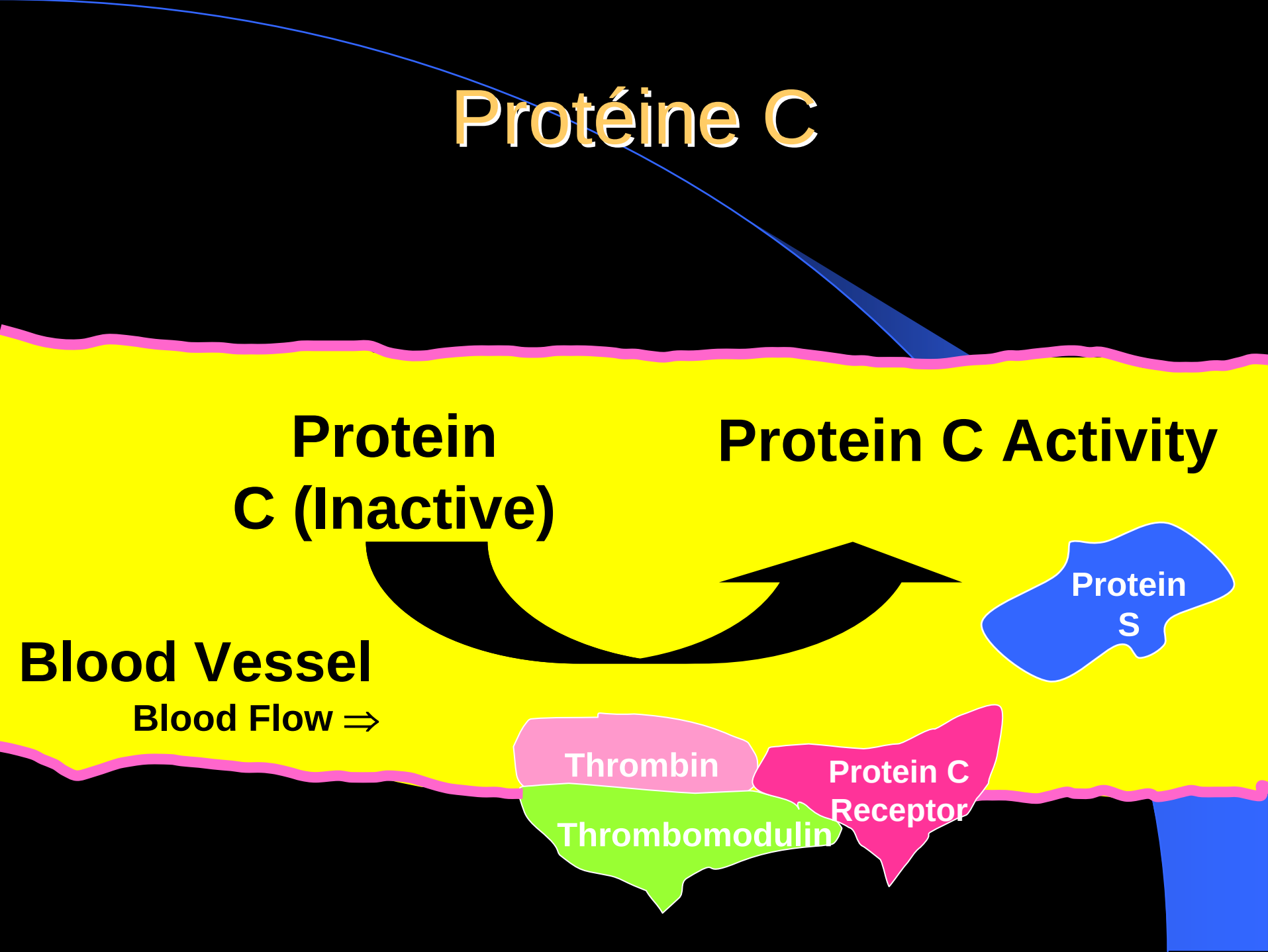
CORTICUS STUDY: effets de la corticothérapie



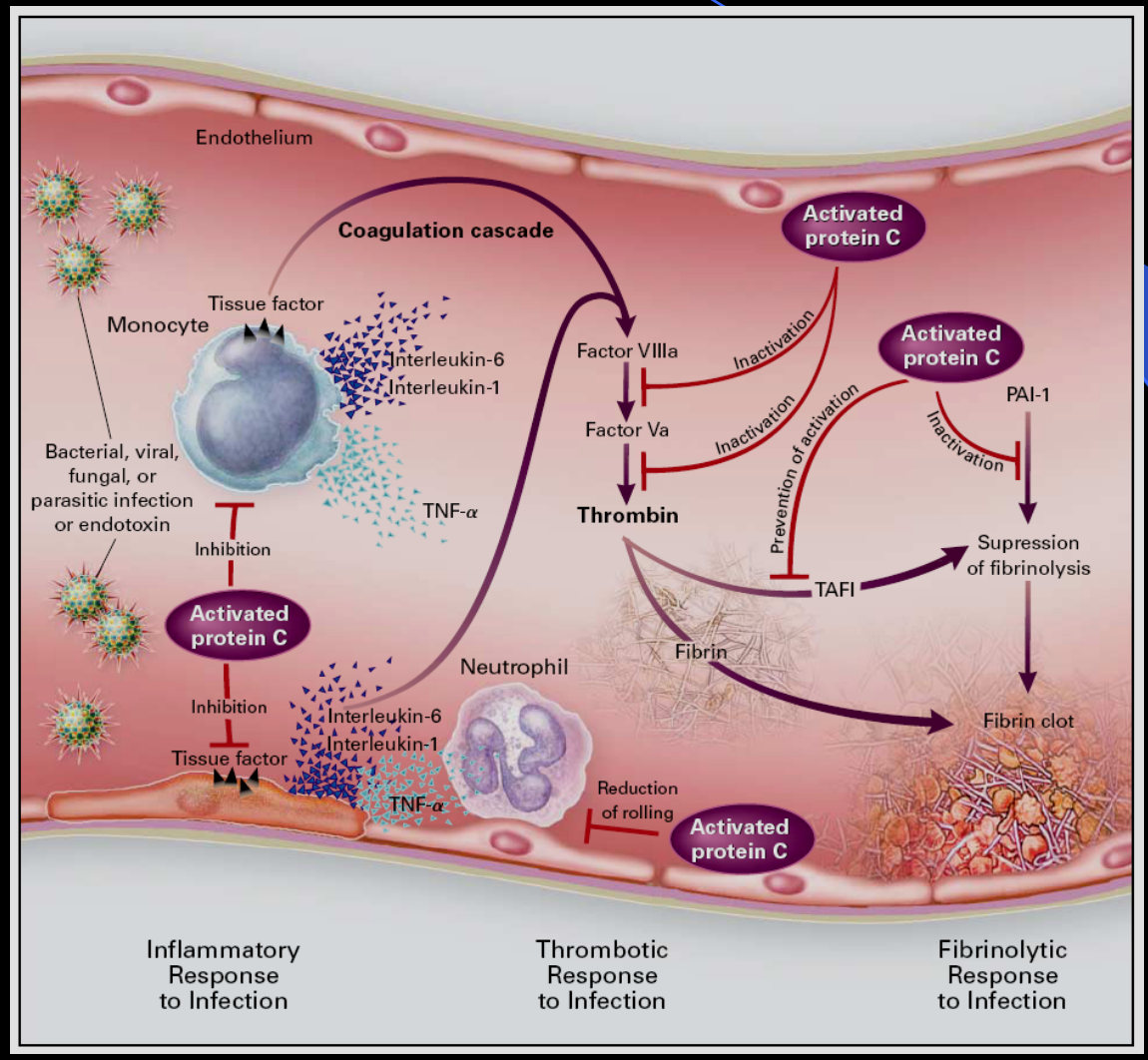
En pratique

- Utilité du test au synacthen controversée: pas d'argument pour réserver les corticoïdes aux non répondeurs mais plutôt aux patients les plus sévères
- Hydrocortisone (Solucortef°) pdt 7 jours chez patients qui nécessitent vasopresseurs si remplissage optimal

Protéine C


Protein
C (Inactive)
Protein C Activity
Protein
S
Blood Vessel
Blood Flow ⇒
Thrombin
Protein C
Receptor
Thrombomodulin

Protéine C


Endothelium
Coagulation cascade
Activated protein C
Tissue factor
Monocyte
Interleukin-6
Interleukin-1
Factor VIIIa
Inactivation
Activated protein C
Factor Va
Inactivation
PAI-1
Bacterial, viral, fungal, or parasitic infection or endotoxin
TNF-α
Thrombin
Prevention of activation
Inactivation
Inhibition
Supression of fibrinolysis
TAFI
Activated protein C
Fibrin
Neutrophil
Inhibition
Interleukin-6
Interleukin-1
Fibrin clot
Tissue factor
TNF-α
Reduction of rolling
Activated protein C
Inflammatory Response to Infection
Thrombotic Response to Infection
Fibrinolytic Response to Infection

The New England Journal of Medicine

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EFFICACY AND SAFETY OF RECOMBINANT HUMAN ACTIVATED PROTEIN C FOR SEVERE SEPSIS

GORDON R. BERNARD, M.D., JEAN-LOUIS VINCENT, M.D., PH.D., PIERRE-FRANCOIS LATERRE, M.D., STEVEN P. LAROSA, M.D., JEAN-FRANCOIS DHAINAUT, M.D., PH.D., ANGEL LOPEZ-RODRIGUEZ, M.D., JAY S. STEINGRUB, M.D., GARY E. GARBER, M.D., JEFFREY D. HELTERBRAND, PH.D., E. WESLEY ELY, M.D., M.P.H., AND CHARLES J. FISHER, JR., M.D., FOR THE RECOMBINANT HUMAN ACTIVATED PROTEIN C WORLDWIDE EVALUATION IN SEVERE SEPSIS (PROWESS) STUDY GROUP*

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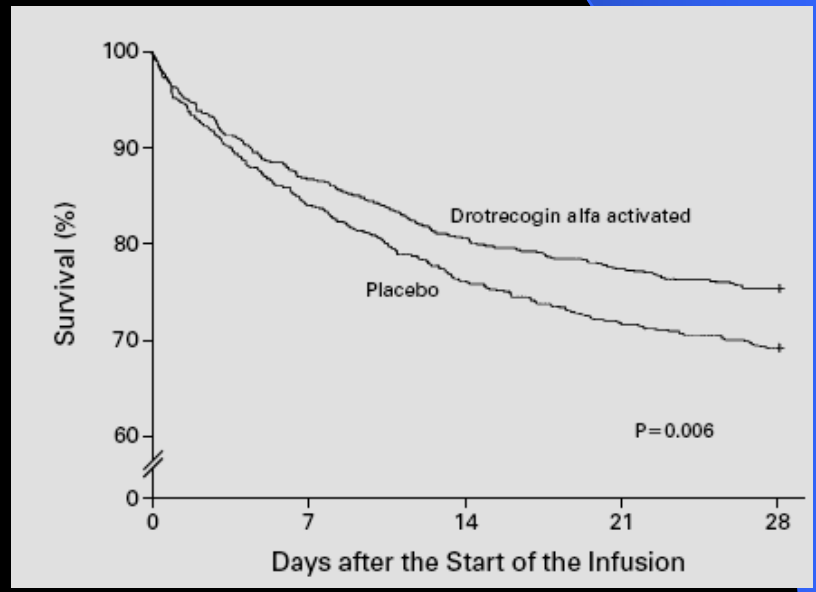
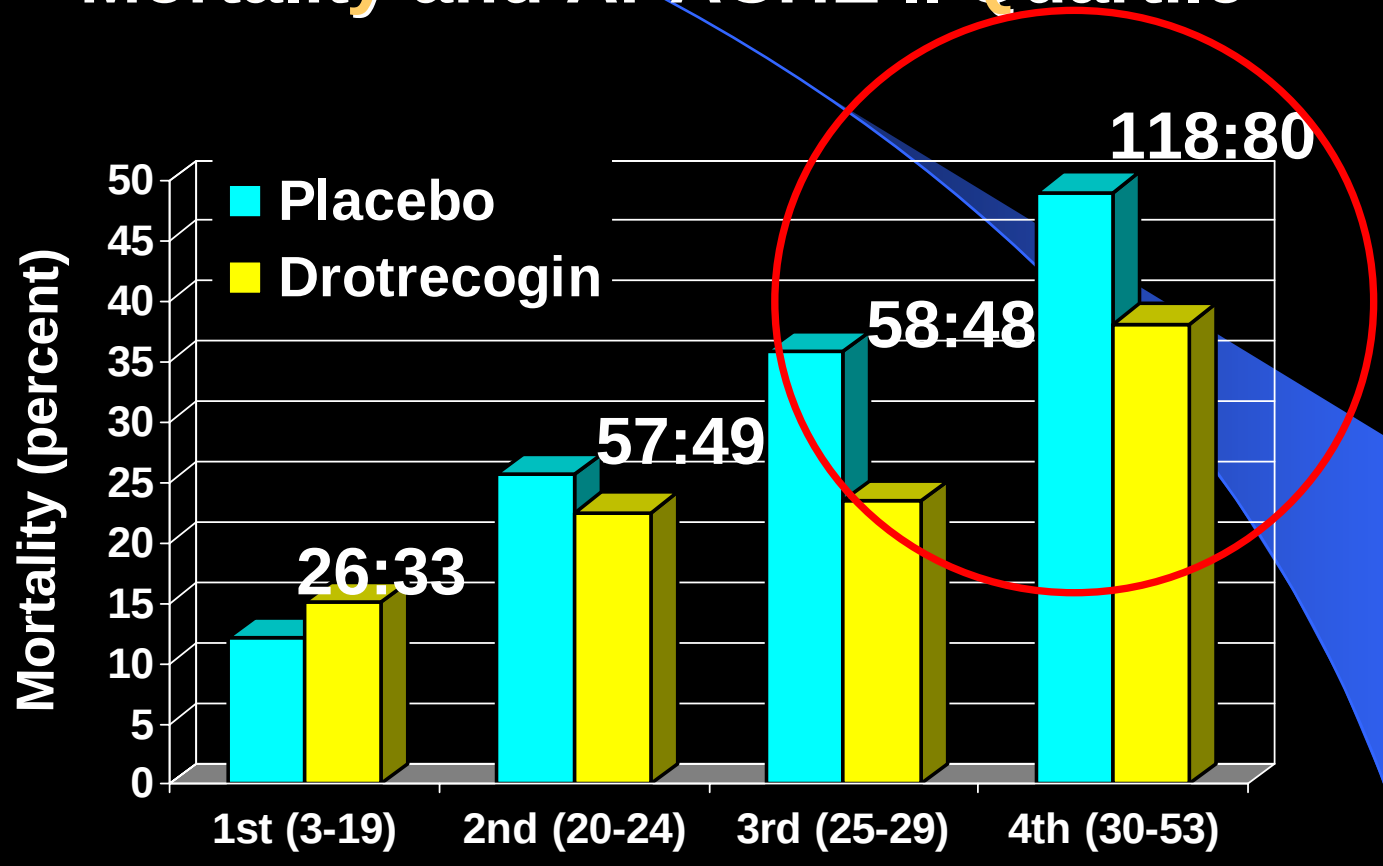
- 1690 patients randomisés, multicentrique, 164 centres, 11 pays: sepsis sévère (avec 3 critères de SIRS et au moins une défaillance d'organe < 24h)
- Réduction de la mortalité de 6.1% (RR 19.4%) à J28



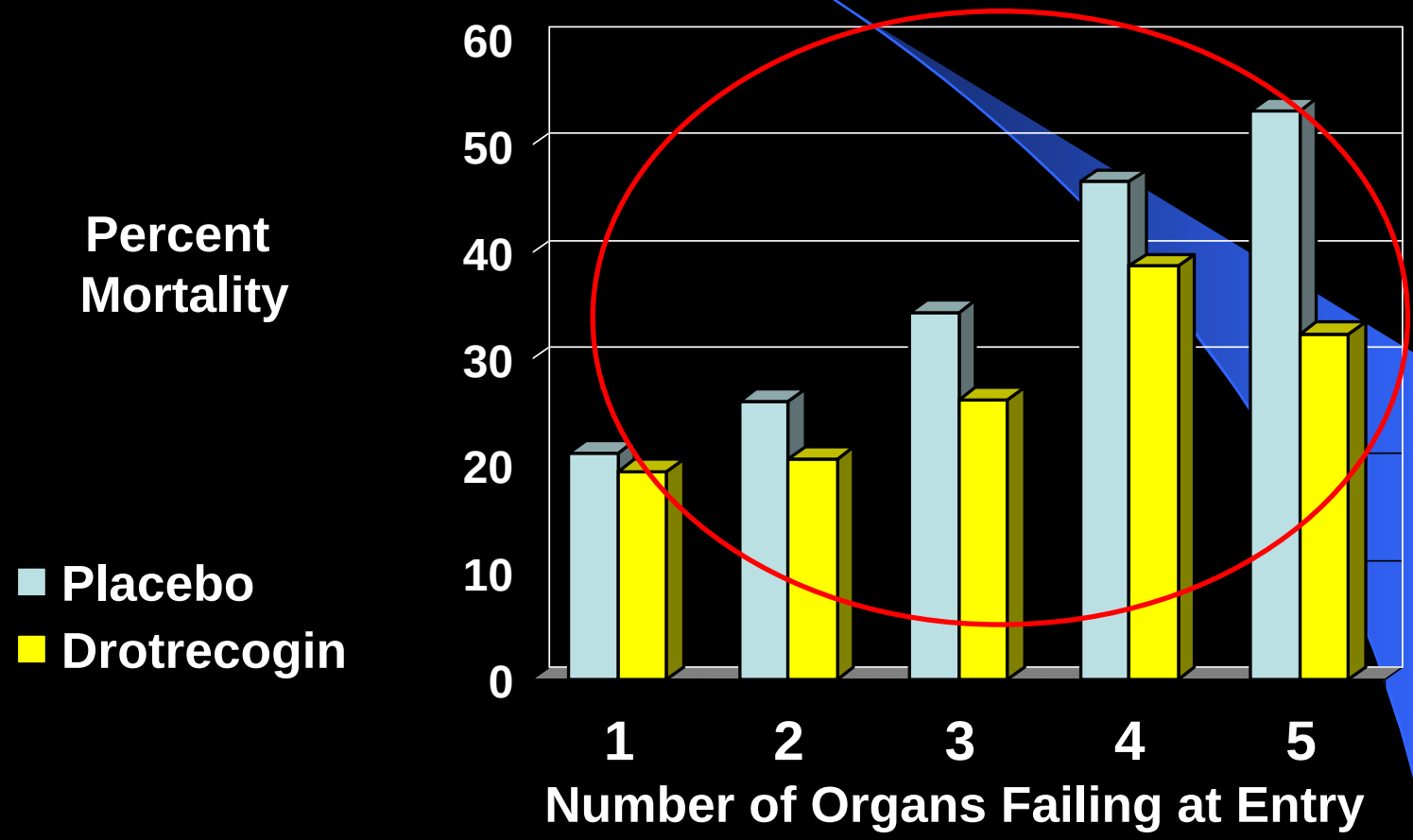
Mortality and APACHE II Quartile



*Numbers above bars indicate total deaths

Bernard GR. Drotrecogin alfa (activated) (recombinant human activated protein C) for the treatment of severe sepsis. *Crit Care Med* 2003; 31[Suppl.]:S85-S90

Mortality and Numbers of Organs Failing



Bernard GR. Drotrecogin alfa (activated) (recombinant human activated protein C) for the treatment of severe sepsis. *Crit Care Med* 2003; 31[Suppl.]:S85-S90

Protéine C activée

- Etude ADDRESS: patients à faible risque de mortalité
- Etude Enhance: confirmer efficacy and safety of the drug

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Drotrecogin Alfa (Activated) for Adults with Severe Sepsis and a Low Risk of Death

Edward Abraham, M.D., Pierre-François Laterre, M.D., Rekha Garg, M.D., Howard Levy, M.D., Ph.D., Deepak Talwar, M.D., Benjamin L. Trzaskoma, M.S., Bruno François, M.D., Jeffrey S. Guy, M.D., Martina Brückmann, M.D., Álvaro Rea-Neto, M.D., Rolf Rossaint, M.D., Dominique Perrotin, M.D., Armin Sablotzki, M.D., Ph.D., Nancy Arkins, R.N., Barbara G. Utterback, M.S., M.B.A., and William L. Macias, M.D., for the Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) Study Group*

N Engl J Med 2005;353:1332-41.

Address

- > 2600 patients randomisés , controlé, double aveugle , multi centrique
- But: effet chez patients à + faible risque de mortalité (Apache < 25, single organ failure)
- 516 centres, 34 pays
- Sepsis sévère avec faible risque de décès càd APACHE II < 25 ou défaillance de un seul organe

Address: Résultats

- Mortalité 20.5 vs 20.6% (NS)

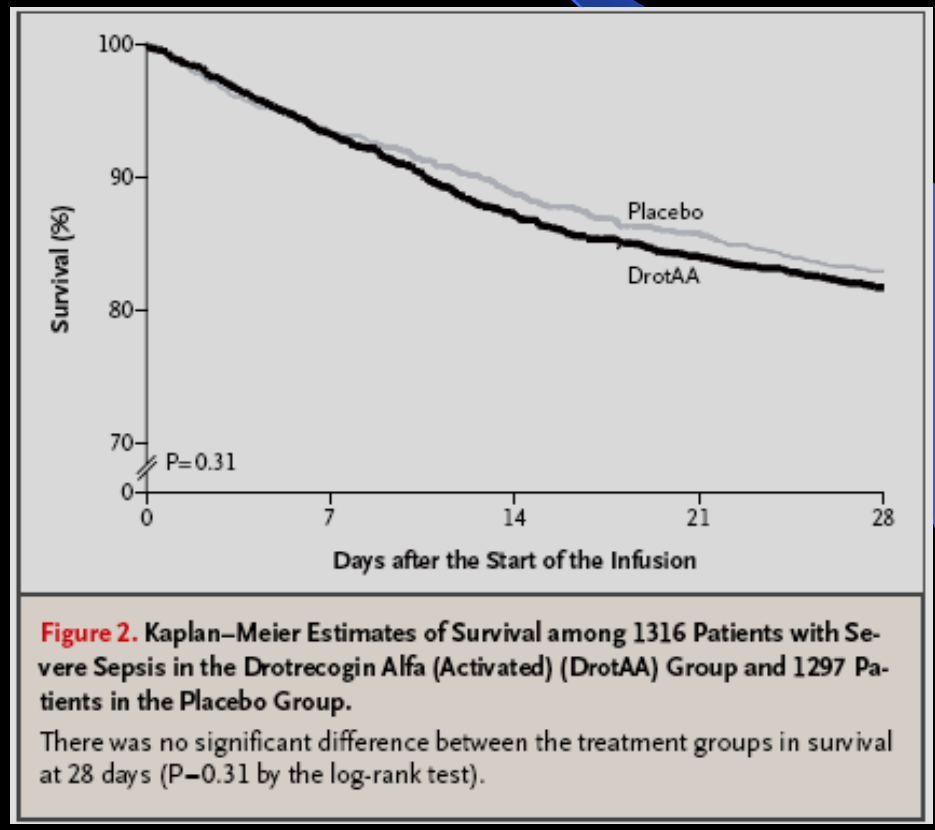


Figure 2. Kaplan–Meier Estimates of Survival among 1316 Patients with Severe Sepsis in the Drotrecogin Alfa (Activated) (DrotAA) Group and 1297 Patients in the Placebo Group.

There was no significant difference between the treatment groups in survival at 28 days (P=0.31 by the log-rank test).

Drotrecogin alfa (activated) treatment in severe sepsis from the global open-label trial ENHANCE: Further evidence for survival and safety and implications for early treatment*

Jean-Louis Vincent, MD, PhD, FCCM; Gordon R. Bernard, MD; Richard Beale, MD; Christopher Doig, MD; Christian Putensen, MD, PhD; Jean-Francois Dhainaut, MD, PhD; Antonio Artigas, MD, PhD; Roberto Fumagalli, MD; William Macias, MD, PhD; Theressa Wright, MD; Kar Wong, PhD; David P. Sundin, PhD; Mary Ann Turlo, RN, MSc; Jonathan Janes, MRCP; for the ENHANCE Study Group

Objective: To provide further evidence for the efficacy and safety of drotrecogin alfa (activated) treatment in severe sepsis.

Design: Single-arm, open-label, trial of drotrecogin alfa (activated) treatment in severe sepsis patients. Enrollment began in March 2001 and day-28 follow-up completed in January 2003.

Setting: ENHANCE took place in 25 countries at 361 sites.

Patients: Patients with known or suspected infection, three or four systemic inflammatory response syndrome criteria, and one or more sepsis-induced organ dysfunctions. Of 2,434 adults entered, 2,378 received drotrecogin alfa (activated), and of these, 2,375 completed the protocol.

Interventions: Drotrecogin alfa (activated) was infused at a dose of 24 μg/kg/hr for 96 hrs.

Measurements and Main Results: The 28-day all-cause mortality approximated that observed in PROWESS (25.3% vs. 24.7%). Although patients in ENHANCE had increased serious bleeding rates compared with patients in the drotrecogin alfa (activated) arm of PROWESS (during infusion, 3.6% vs. 2.4%; postinfusion, 3.2% vs. 1.2%; 28-day, 6.5% vs. 3.5%), increased postinfusion bleeding suggested a higher background bleeding rate. Intracranial hemorrhage was more common in ENHANCE than PROWESS (during infusion, 0.6% vs. 0.2%; 28-day, 1.5% vs. 0.2%). The incidence of fatal intracranial hemorrhage was the same during infusion (0.2%) and higher at 28 days (0.5% vs. 0.2%). ENHANCE patients treated within 0–24 hrs from their first sepsis-induced organ dysfunction had lower observed mortality rate than those treated after 24 hrs (22.9% vs. 27.4%, $p = .01$).

Conclusions: ENHANCE provides supportive evidence for the favorable benefit/risk ratio observed in PROWESS and suggests that more effective use of drotrecogin alfa (activated) might be obtained by initiating therapy earlier. (Crit Care Med 2005; 33:2266–2277)

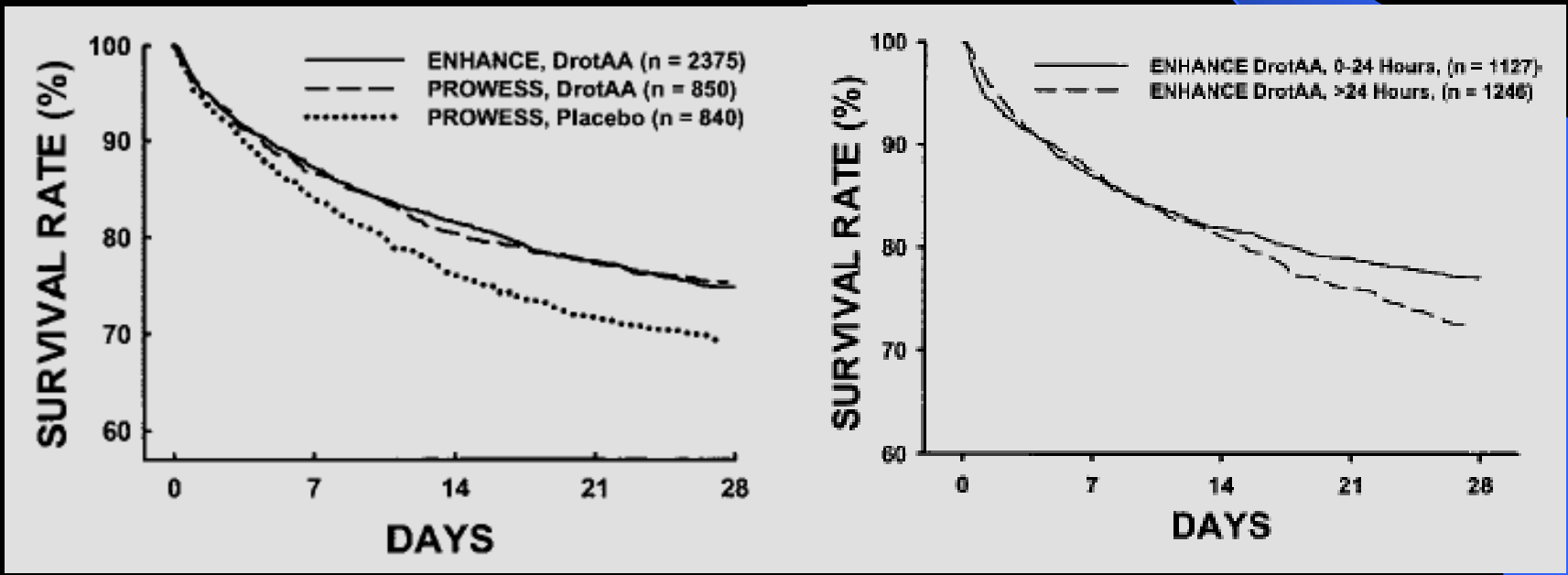
KEY WORDS: severe sepsis; drotrecogin alfa (activated); activated protein C; early treatment; ENHANCE; clinical trial

Enhance

- 2375 patients
- 25 pays 361 sites, étude ouverte un seul bras
- But: obtenir plus de données sur la sécurité et efficacité du traitement
- Sepsis sévère avec une ou plusieurs défaillances d'organe

Résultats

- Mortalité identique à l'étude Prowess



Résultats

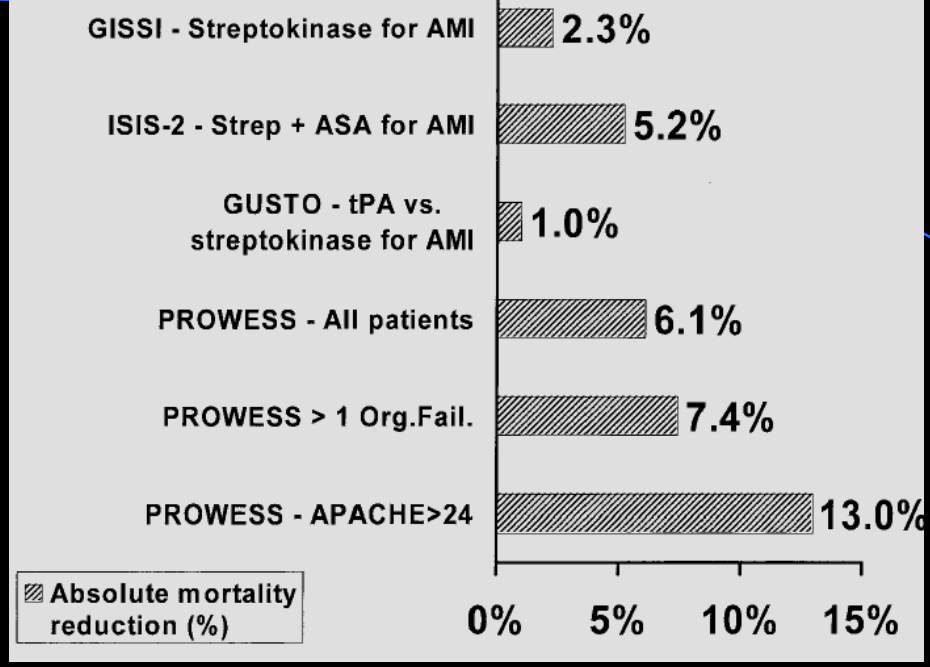
- Saignement un peu plus importants que dans Prowess, mais aussi après la période d'infusion de 96h (population différente: plus chirurgicale, plus dysfonction hématologique)

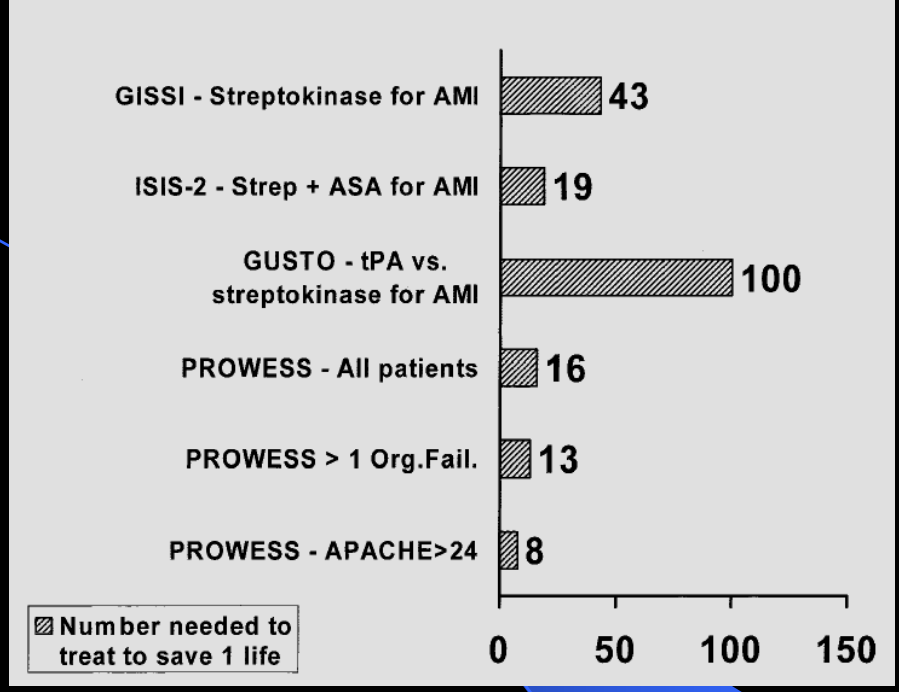
Enhance: conclusions

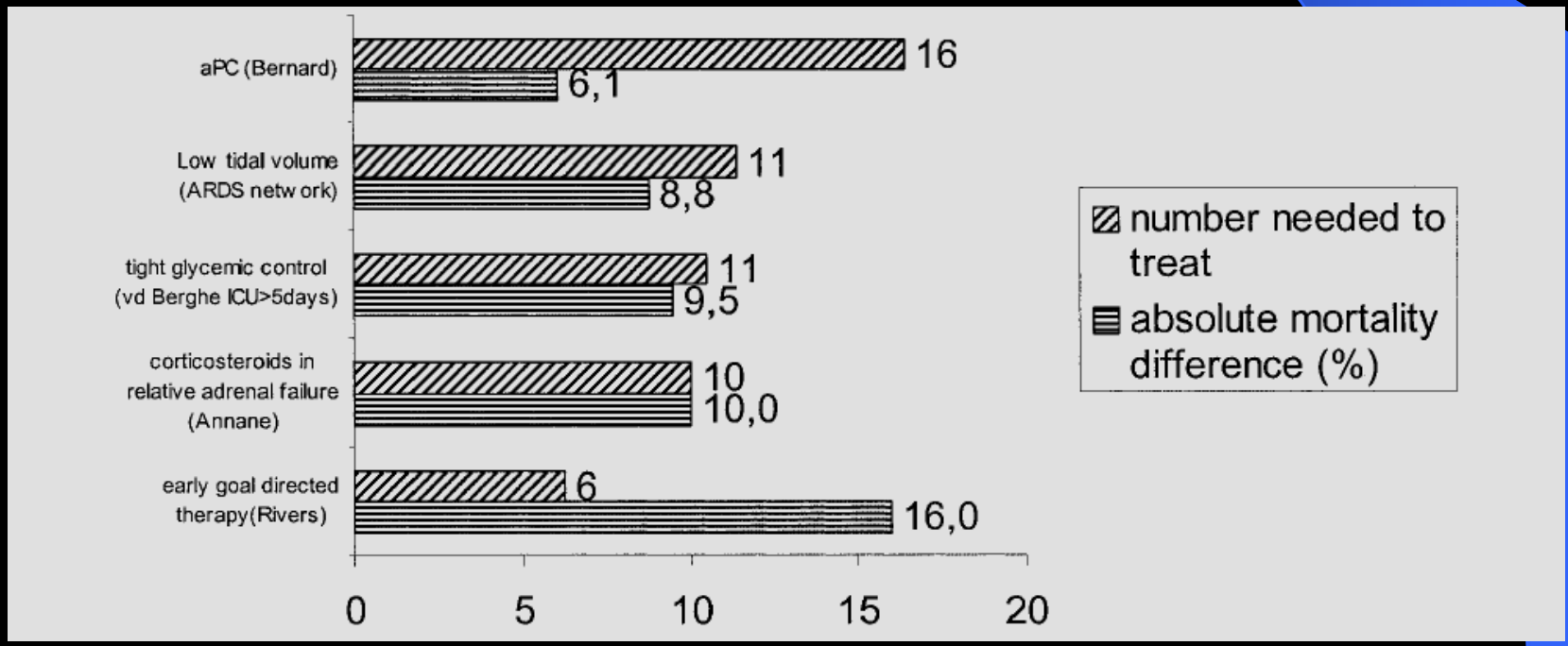
- Confirme les données de Prowess
- Saignements un peu plus importants mais risque reste acceptable
- Meilleurs résultats quand traitement démarré dans les 24h.

Pro/ con

- Coût bénéfice (27.400 $ cost per quality-adjusted life-year) NNT = 16
- Risque de saignement (3.5% vs 2% in Prowess)
- Efficacité chez low risk, chez l'enfant
- Variabilité dans efficacité au cours du déroulement de l'étude (plus efficace dans la deuxème partie)
- ATIII et TFPI inefficace: pourtant actif aussi en réduisant la formation de thrombine

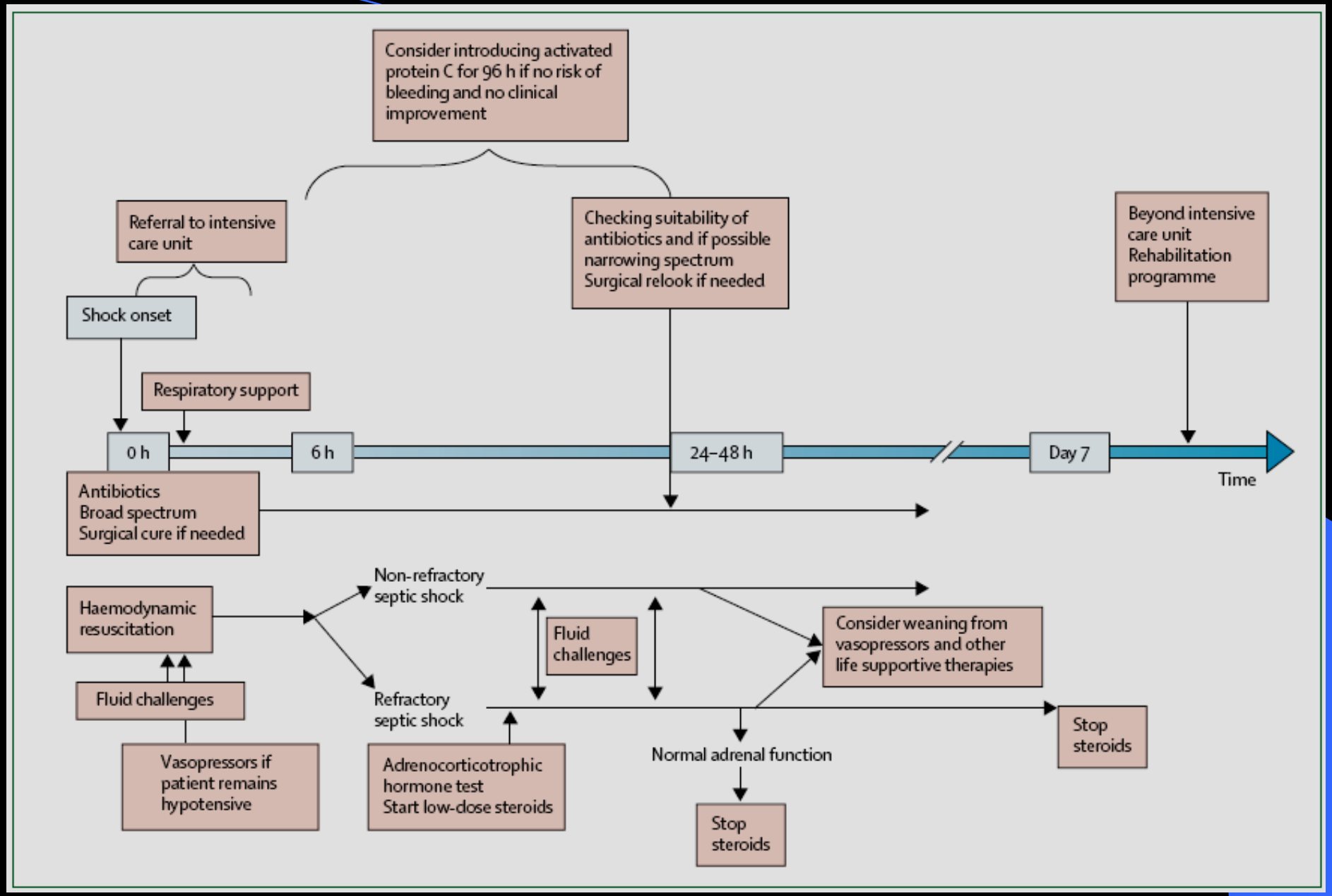

GISSI - Streptokinase for AMI
2.3%
ISIS-2 - Strep + ASA for AMI
5.2%
GUSTO - tPA vs. streptokinase for AMI
1.0%
PROWESS - All patients
6.1%
PROWESS > 1 Org.Fail.
7.4%
PROWESS - APACHE>24
13.0%
Absolute mortality reduction (%)
0%
5%
10%
15%


GISSI - Streptokinase for AMI
43
ISIS-2 - Strep + ASA for AMI
19
GUSTO - tPA vs. streptokinase for AMI
100
PROWESS - All patients
16
PROWESS > 1 Org.Fail.
13
PROWESS - APACHE>24
8
Number needed to treat to save 1 life
0
50
100
150


aPC (Bernard)
16
6,1
Low tidal volume (ARDS network)
11
8,8
tight glycemic control (vd Berghe ICU>5days)
11
9,5
corticosteroids in relative adrenal failure (Annane)
10
10,0
early goal directed therapy(Rivers)
6
16,0
0
5
10
15
20
number needed to treat
absolute mortality difference (%)

Indications Xigris en Belgique

- Sepsis sévère avec deux défaillances d'organe depuis moins de 24 heures:
  - Hypotension malgré remplissage nécessitant vasopresseur
  - PaO2/FiO2 < 250 ou ventilation mécanique depuis moins de 72h
  - Oligurie < 0.5 ml/kg/h pdt au moins une heure malgré remplissage adéquat
  - Chute de PLT < 100.000 ou de 50%
  - Lactate (>1.5 norm) avec EB < -5 ou pH < 7.3
- >18 ans, pas anticoagulé, pas fibrinolysé <3j, GIIbIIIa <7j, PLT >30.000, …


Consider introducing activated protein C for 96 h if no risk of bleeding and no clinical improvement
Referral to intensive care unit
Checking suitability of antibiotics and if possible narrowing spectrum
Surgical relook if needed
Beyond intensive care unit
Rehabilitation programme
Shock onset
Respiratory support
0 h
6 h
24–48 h
Day 7
Time
Antibiotics
Broad spectrum
Surgical cure if needed
Haemodynamic resuscitation
Non-refractory septic shock
Fluid challenges
Consider weaning from vasopressors and other life supportive therapies
Fluid challenges
Refractory septic shock
Stop steroids
Vasopressors if patient remains hypotensive
Adrenocorticotrophic hormone test
Start low-dose steroids
Normal adrenal function
Stop steroids

En résumé: sepsis resuscitation bundle

- **A la première heure**: reconnaissance de l'infection et des signes de gravité associés (sepsis team?), monitoring non invasif (PA, Sp O2), lactate, contacter USI pour avis
- Lactate
- Hémocultures avant administration antibiotiques
- Antibiothérapie probabiliste (dans les 3h)
- Si hypotension (PAS < 90 ou PAM < 70) ou lactate > 4 mmol/L
  - Expansion volémique
  - Vasopresseurs si PAM < 65 malgré expansion volémique
- Si hypotension ou lactate persistent:
  - Maintenir PVC 8-12
  - Inotrope (si Htc < 30% => d'abord transfusion), si SVcO2 < 70%, SvO2 < 65% et PVC > 8 mmHg

En résumé: sepsis management bundle

- Low dose of steroid
- Protéine C activée
- Contrôle glycémique
- Eviter pression plateau élevée

+ maintien des objectifs hémodynamiques, adaptation de l'ABTH, réduction des vasopresseurs dès que possible,

Est-ce utile?

Continuing Medical Education Article

Economic implications of an evidence-based sepsis protocol: Can we improve outcomes and lower costs?*

Andrew F. Shorr, MD, MPH; Scott T. Micek, PharmD; William L. Jackson, Jr, MD; Marin H. Kollef, MD

Objective: To determine the financial impact of a sepsis protocol designed for use in the emergency department.

Design: Retrospective analysis of a before-after study testing the implications of sepsis protocol.

Setting: Academic, tertiary care hospital in the United States.

Patients: Persons with septic shock presenting to the emergency department.

Interventions: A multifaceted protocol developed from recent scientific literature on sepsis and the Surviving Sepsis Campaign. The protocol emphasized identification of septic patients, aggressive fluid resuscitation, timely antibiotic administration, and appropriateness of antibiotics, along with other adjunctive, supportive measures in sepsis care.

Measurements and Main Results: We compared patients treated before the protocol with those cared for after the protocol was implemented. Overall hospital costs represented the primary end point, whereas hospital length of stay served as a secondary end point. All hospital costs were calculated based on charges after conversion to costs based on department-specific cost-to-charge ratios. We also attempted to measure the independent impact of the protocol on costs through linear regression. We conducted a sensitivity analysis assessing these end points in the subgroup of subjects who survived their hospitalization. The total cohort included 120 subjects (evenly divided into the before and after cohorts) with a mean age of 64.7 ± 18.2 yrs and median Acute Physiology and Chronic Health Evaluation II score of 22.5 ± 8.3. There were more survivors following the protocol's adoption (70.0% vs. 51.7%, $p = .040$). Median total costs were significantly lower with use of the protocol ($16,103 vs. $21,985, $p = .008$). The length of stay was also on average 5 days less among the postintervention population ($p = .023$). A Cox proportional hazard model indicated that the protocol was independently associated with less per-patient cost. Restricting the analysis to only survivors did not appreciably change our observations.

Conclusions: Use of a sepsis protocol can result not only in improved mortality but also in substantial savings for institutions and third party payers. Broader implementation of sepsis treatment protocols represents a potential means for enhancing resource use while containing costs. (Crit Care Med 2007; 35:●●●–●●●)

Key Words: cost; economics; outcomes; protocol; sepsis

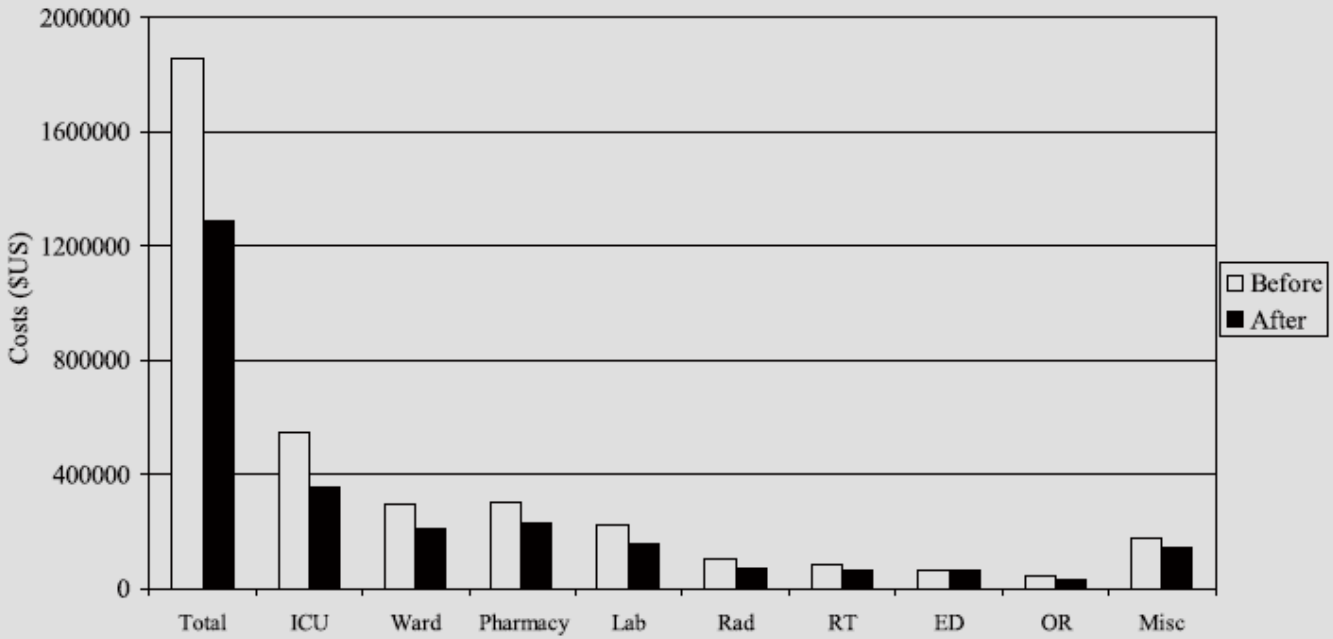


Figure 2. Distribution of total and component costs for patients treated before and after protocol implementation. *ICU*, intensive care unit; *Lab*, laboratory; *Rad*, radiology; *RT*, respiratory therapy; *ED*, emergency department; *OR*, operating room.

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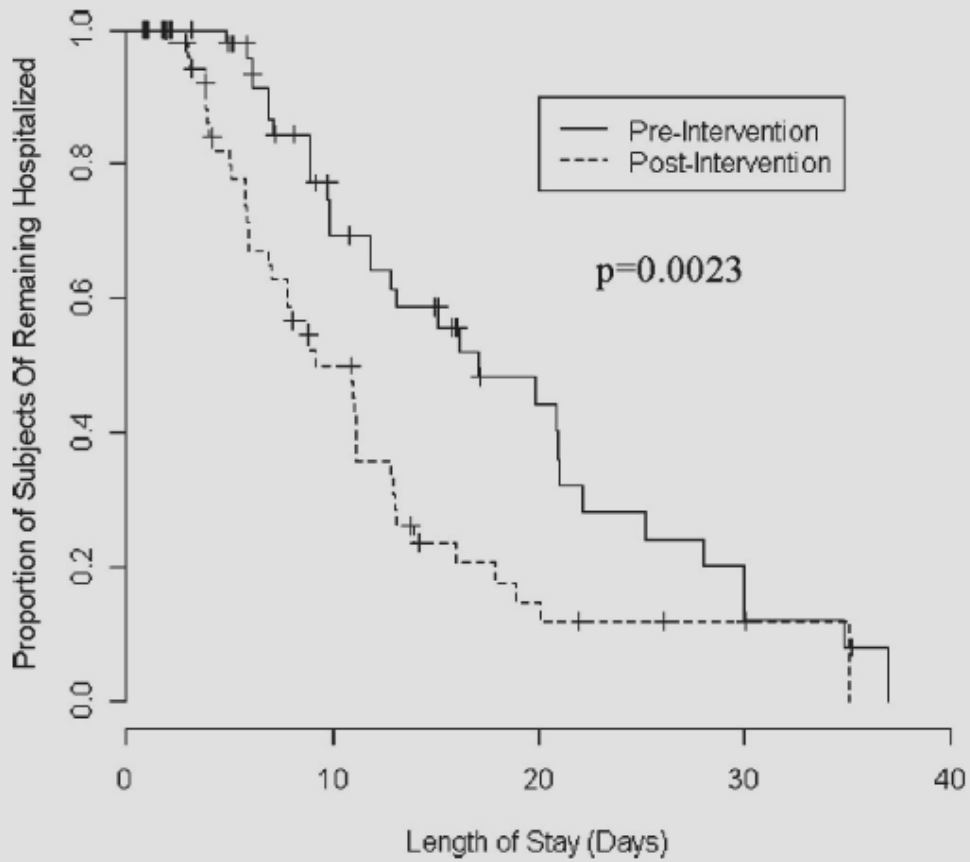


Figure 3. Kaplan-Meier plot showing proportion of patients hospitalized over time before and after implementation of the protocol.

Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality*

H. Bryant Nguyen, MD, MS; Stephen W. Corbett, MD, PhD; Robert Steele, MD; Jim Banta, PhD, MPH; Robin T. Clark, BS; Sean R. Hayes; Jeremy Edwards; Thomas W. Cho, MD; William A. Wittlake, MD

Objective: The purpose of this study was to examine the outcome implications of implementing a severe sepsis bundle in an emergency department as a quality indicator set with feedback to modify physician behavior related to the early management of severe sepsis and septic shock.

Design: Two-year prospective observational cohort.

Setting: Academic tertiary care facility.

Patients: Patients were 330 patients presenting to the emergency department who met criteria for severe sepsis or septic shock.

Interventions: Five quality indicators comprised the bundle for severe sepsis management in the emergency department: a) initiate central venous pressure (CVP)/central venous oxygen saturation ($Scvo_2$) monitoring within 2 hrs; b) give broad-spectrum antibiotics within 4 hrs; c) complete early goal-directed therapy at 6 hrs; d) give corticosteroid if the patient is on vasopressor or if adrenal insufficiency is suspected; and e) monitor for lactate clearance.

Measurements and Main Results: Patients had a mean age of 63.8 ± 18.5 yrs, Acute Physiology and Chronic Health Evaluation II score 29.6 ± 10.6, emergency department length of stay 8.5 ± 4.4 hrs, hospital length of stay 11.3 ± 12.9 days, and in-hospital mortality 35.2%. Bundle compliance increased from zero to 51.2% at the end of the study period. During the emergency department stay, patients with the bundle completed received more CVP/$Scvo_2$ monitoring (100.0 vs. 64.8%, $p < .01$), more antibiotics (100.0 vs. 89.7%, $p = .04$), and more corticosteroid (29.9 vs. 16.2%, $p = .01$) compared with patients with the bundle not completed. In a multivariate regression analysis including the five quality indicators, completion of early goal-directed therapy was significantly associated with decreased mortality (odds ratio, 0.36; 95% confidence interval, 0.17–0.79; $p = .01$). In-hospital mortality was less in patients with the bundle completed compared with patients with the bundle not completed (20.8 vs. 39.5%, $p < .01$).

Conclusions: Implementation of a severe sepsis bundle using a quality improvement feedback to modify physician behavior in the emergency department setting was feasible and was associated with decreased in-hospital mortality. (Crit Care Med 2007; 35:1105–1112)

KEY WORDS: sepsis bundle; sepsis quality indicators; early goal-directed therapy; emergency department

Table 1. Severe sepsis bundle and inherent quality indicators

6-hr emergency department severe sepsis bundle

1. Initiate CVP/$Scvo_2$ monitoring within 2 hrs of meeting bundle criteria
2. Give broad-spectrum antibiotics within 4 hrs of meeting bundle criteria
3. Complete early goal-directed therapy (CVP ≥8 mm Hg, SBP ≥90 mm Hg or MAP ≥65 mm Hg, and $Scvo_2$ ≥70%) at 6 hrs of meeting bundle criteria
4. Give steroid if patient is on vasopressor or if adrenal insufficiency is suspected
5. Monitor for lactate clearance

Completion of the bundle is defined as completion of quality indicators 1, 2, and 3 and one or more of items 4 and 5

The criteria to initiate the bundle are the following

1. Two or more of the following four items
   a. Temperature >38.3°C or <36.0°C
   b. Heart rate >90 beats/min
   c. Respiration >20 breaths/min
   d. White blood cell count >12,000 or <4000/mm^3, or >10% bandemia
2. A suspected infection
3. SBP <90 mm Hg after 20-mL/kg fluid bolus or lactate ≥4 mmol/L

CVP, central venous pressure; $Scvo_2$, central venous oxygen saturation; SBP, systolic blood pressure; MAP, mean arterial pressure.

Percentage compliance during an implementation phase (i.e., a 3-month period) was defined as the number of patients completing the particular bundle quality indicator (or the *numerator*) divided by the number of patients meeting the criteria for initiation of the bundle (or the *denominator*).

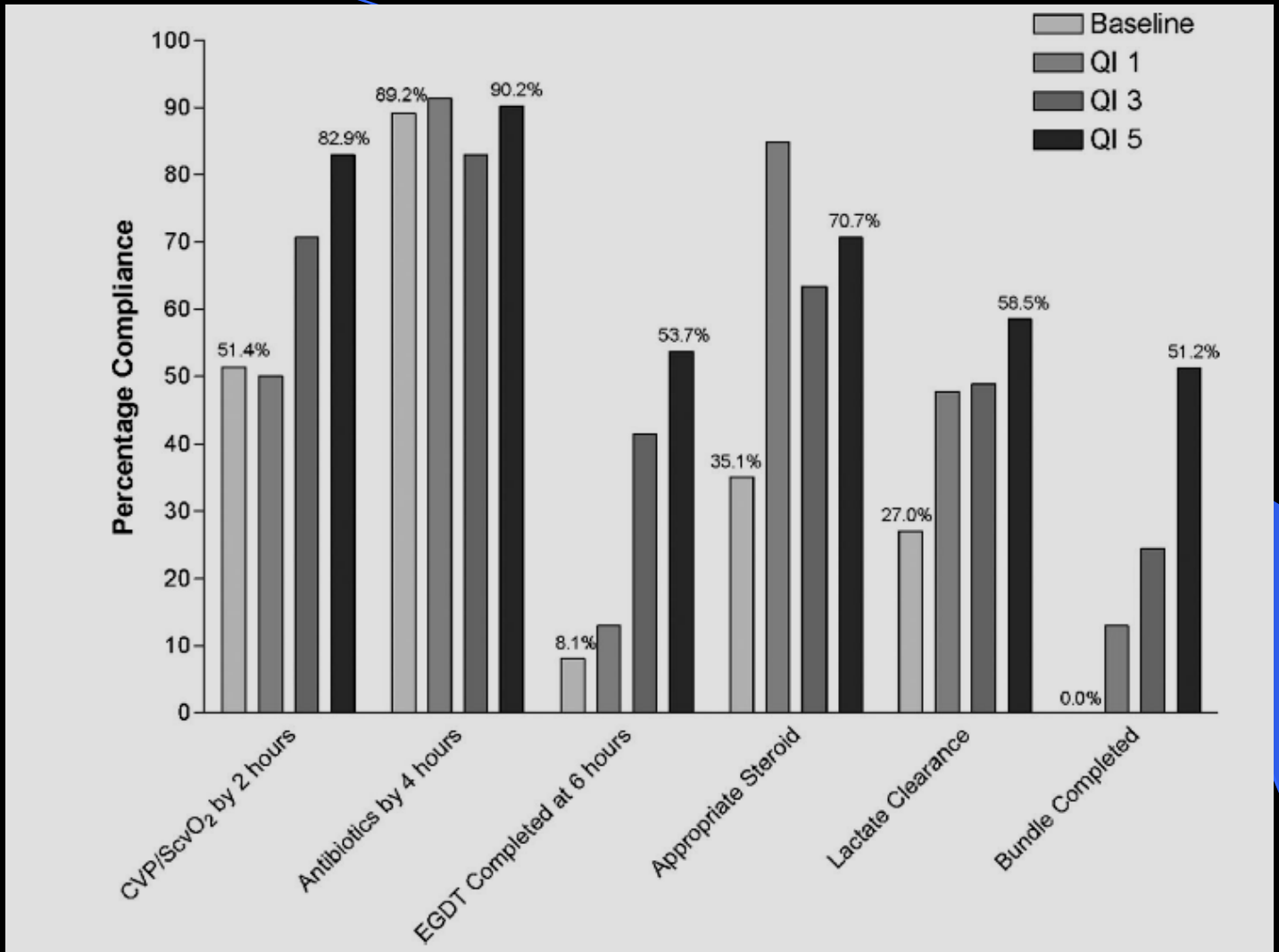
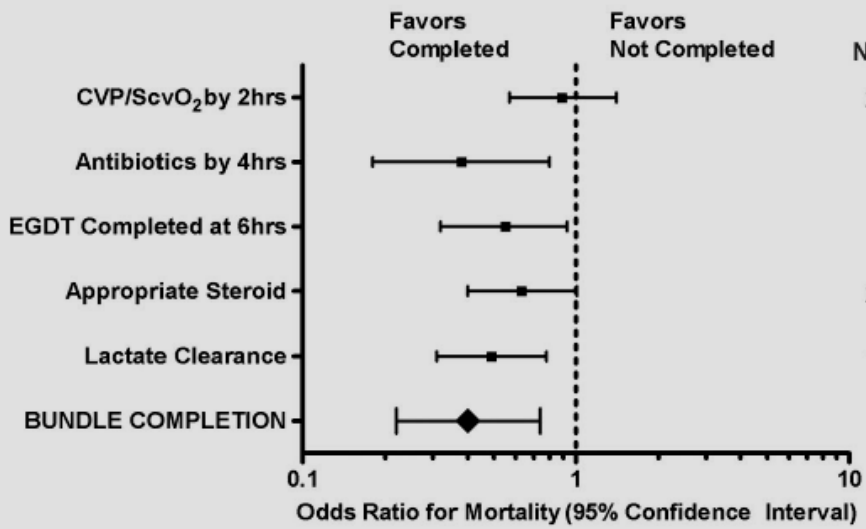


Figure 1. Bundle percentage compliance from baseline through the quality improvement phases. Each phase represents percentage compliance in the bundle quality indicators over a 3-month period. *QI*, quality improvement; *CVP*, central venous pressure; *$Scvo_2$*, central venous oxygen saturation; *EGDT*, early goal-directed therapy.



	In-Hospital Mortality (%)		
No. Patients*	Completed	Not Completed	P-value
208 vs. 122	33.8	36.4	0.65
298 vs. 32	32.9	56.0	0.03
93 vs. 237	25.8	38.8	0.03
208 vs. 122	31.3	41.8	0.06
160 vs. 170	26.9	42.9	<0.01
77 vs. 253	**20.8**	**39.5**	**<0.01**

*Number of patients (out of 330 total patients) completing vs. not completing the quality indicator

Figure 2. Odds ratio for in-hospital mortality relative to completion of each bundle quality indicator and completion of the bundle. *CVP*, central venous pressure; *$Scvo_2$*, central venous oxygen saturation; *EGDT*, early goal-directed therapy.

L'avenir…

- Adapter le traitement en fonction du patient (c'est déjà un peu ce que l'on fait qd on interroge le patient sur ces ATCD hérditaires!)
- Le concept PIRO

PIRO concept

Domain	Present	Future	Rationale
Predisposition	Premorbid illness with reduced probability of short term survival. Cultural or religious beliefs, age, sex.	Genetic polymorphisms in components of inflammatory response (e.g., TIR, TNF, IL-1, CD14); enhanced understanding of specific interactions between pathogens and host diseases.	In the present, premorbid factors impact on the potential attributable morbidity and mortality of an acute insult; deleterious consequences of insult heavily dependent on genetic predisposition (future).
Insult infection	Culture and sensitivity of infecting pathogens; detection of disease amenable to source control.	Assay of microbial products (LPS, mannan, bacterial DNA); gene transcript profiles.	Specific therapies directed against inciting insult require demonstration and characterization of that insult.
Response	SIRS, other signs of sepsis, shock, CRP.	Nonspecific markers of activated inflammation (e.g., PCT or IL-6) or impaired host responsiveness (e.g., HLA-DR); specific detection of target of therapy (e.g., protein C, TNF, PAF).	Both mortality risk and potential to respond to therapy vary with nonspecific measures of disease severity (e.g., shock); specific mediator-targeted therapy is predicated on presence and activity of mediator.
Organ dysfunction	Organ dysfunction as number of failing organs or composite score (e.g., MODS, SOFA, LODS, PEMOD, PELOD).	Dynamic measures of cellular response to insult—apoptosis, cytopathic hypoxia, cell stress.	Response to preemptive therapy (e.g., targeting microorganism or early mediator) not possible if damage already present; therapies targeting the injurious cellular process require that it be present.

TLR, Toll-like receptor; TNF, tumor necrosis factor; IL, interleukin; LPS, lipopolysaccharide; SIRS, systemic inflammatory response syndrome; CRP, C-reactive protein; PCT, procalcitonin; HLA-DR, human leukocyte antigen-DR; PAF, platelet-activating factor; MODS, multiple organ dysfunction syndrome; SOFA, sepsis-related organ failure assessment; LODS, logistic organ dysfunction system; PEMOD, pediatric multiple organ dysfunction; PELOD, pediatric logistic organ dysfunction.

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La variabilité génétique

- Polymorphisme génétique:
  - Single nucléotide polymorphisme (SNIP): il y en a 10.000.000
  - Une base en plus ou en moins: il y en a 3.000.000

  90% des polymorphismes sont situés entre les gènes (peu d'effet)

  10% sont dans les gènes

polymorphisme

- Effet au niveau de la reconnaissance:
  - CD-14 Sutherland CCM 2005 CD-14 severe sepsis susceptibility
- Protéines de l'inflammation:
  - IRAK-1 AJRCCM 2006 175-1335 IRAK-1 haplotype increase NF-Kappa B activity
  - TNF: différents polymorphismes responsables d'une augmentation de la secrétion (Eur Resp Journal 2005 Gong MN)
- Coagulation: CCM 2006 Walley prot C : génotype AA => prot C diminuée => diminue survie

La variabilité génétique

- La race (noir plus susceptible que les blancs aux infections)

Nouvelles techniques appliquées au choc septique

- Protéomique: étude globale des protéines dans 1 milieu biologique
  - proANP (seristra°), proadrénomodulline (Sevadil°) = facteur de rique de sévérité dans infection
- Cytométrie de flux: analyse des cell en suspension permet de détecter des marqueurs à la surf des cell:
  - CD 64 recepteur IgG: marqueur de l'infect° bact à la surf des polynucléaires
  - HLA DR sur monocytes: sensible à tous les médiateurs largués au cours du choc septique: IL10 et cortisol diminue le HLA DR, TNF et Interferon l'augmente (Monneret et al ICM 2006); infection nosocomiale plus fréquente si HLA DR bas.

Etudes en cours

- Genosept: pneumonie, pancréatite, péritonite
- IMPACT:
- PNEUMAGENE
- GENIMS: Genetic and inflammatory markers of Sepsis (Pittsburgh)
- GEN SEP GROUP

A l'avenir

- Établir le risque individuel pour permettre une meilleure prévention
- Compendre ce qui se passe à l'échelle d'un individu
- Scores de gravités adaptés
- Etude sur les traitements adaptés